

Appendix
Volume I

The Belmont Report

Ethical Principles
and Guidelines for
the Protection of
Human Subjects
of Research

The National Commission
for the Protection of Human Subjects
of Biomedical and Behavioral
Research

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The National Commission
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Research

This Appendix contains (in two volumes)
the full text of the papers that were prepared
to assist the Commission in its consideration
of the basic ethical principles that should
underlie the conduct of research
involving human subjects.

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I

PRELIMINARY PAPERS PREPARED FOR THE COMMISSION
BY ROBERT J. LEVINE, M.D.

1

THE BOUNDARIES BETWEEN BIOMEDICAL OR BEHAVIORAL
RESEARCH AND THE ACCEPTED AND ROUTINE
PRACTICE OF MEDICINE

Robert J. Levine, M.D.

July 14, 1975

The Commission is charged with the responsibility to consider, among other things, (i) The boundaries between biomedical or behavioral research involving human subjects and the accepted and routine practice of medicine. It is fortunate that sharp definitions of the boundaries are not required. Even a superficial exploration of this problem (contained in this paper) will reveal the impossibility of describing mutually exclusive subsets (one called research and one called practice) of the universe of activities in which health care professionals may be engaged. It will be possible to describe some activities as pure research and some other activities as pure practice; these activities will be defined but not discussed in this paper. The focus of this paper will be on activities having one or more of the following characteristics:

- 1) there may be legitimate dispute as to whether they are research or practice;
- 2) there is no dispute that they are combinations of research and practice; or
- 3) there may be some confusion in the view of one or more of the participants in the process as to whether the activity is either research or practice or a combination thereof.

The purpose of the considerations

What is the point in considering the boundaries between research and the practice of medicine? To what use will such considerations be put? Let us first agree that we do not know the answers to these questions. Alternatively, let us first agree that each party to these considerations is likely at the outset to answer these questions somewhat differently from each other. There are those who assume that the final recommendations of the Commission will indicate that different sorts of protections are required for subjects (the subjects of the research activities of investigators) than are required for patients

(the clients of health care professionals). To that others will respond that the Commission has been further charged to "...consider the appropriateness of applying the principles and guidelines identified and developed under subparagraph (A) to the delivery of health services to patients...". (This issue will be the subject of another staff paper.)

There are those who will assume that the requirements for informed consent are greater for subjects than they are for patients. To this one may respond that in many recent malpractice litigations the physician has been found "negligent" for having failed to provide "full disclosure". All of these cases have been in the context of practice, not research.

Another assumption from which one might proceed is that it is necessary to identify research so that a determination might be made as to what sorts of activities should be reviewed by institutional review boards. Technically, this assumption cannot now be challenged. Yet there are in most institutions devoted to practice various panels, committees, and boards similarly charged to review the practice activities within those institutions. Ongoing review of practice activities is beginning under Professional Standards Review Organizations (PSROs). So, perhaps one purpose of these considerations is to determine which activities are the proper turf of which review body.

There are many other assumptions that might be stated and challenged at the outset. They all have in common that research could or should be seen as somehow differing from practice. As the Commission focuses on its primary purpose--that contained in its title--the Protection of Human Subjects--the ultimate focus of this paper becomes more clear. The purpose of defining the boundaries between research and practice is to determine where one might find research subjects to

protect. The extent to which the protections required for research subjects may differ from those required for patients remains to be determined. This paper is written with the assumption that patients and subjects should be treated somewhat differently. At the very least the individual should be aware of which role he (or she) is playing--or being asked to play--and what the implications are of playing the role of subject as opposed to patient.

Patients and subjects (definitions)

At this point the words patient and subject--as they are used in this paper--will be defined; then there will be a brief statement of some of the assumptions that derive from these definitions. As the paper develops the distinctions between patients and subjects should become increasingly clear and the ramifications of the assumptions contained in these definitions should seem increasingly important.

A patient is a client of a health care professional. By contrast, a subject is an individual who is observed or experimented with by an investigator. In determining the interactions between the individual (patient or subject) and the professional (health care professional or investigator) the final decision-making authority resides in the non professional. However, the patient may ordinarily assume that the health care professional will be acting in his (or her) best interests. Thus, in ordinary circumstances, the patient may choose to delegate decision-making authority to the health care professional to whatever extent he (or she) wishes. Ideally, he should be aware that he may withdraw this delegation of authority whenever it seems appropriate. For example, he

might seek consultation with another health care professional. The responsible health care professional will, in fact, advise the patient when it might be appropriate to withdraw delegation of decision-making authority for any of a variety of reasons. The subject, on the other hand, should feel very less secure in delegating decision-making authority to the investigator. While the health care professional might be assumed to see the well-being of the patient as the most important end, the investigator is assumed to see development of new knowledge as a major, if not the ultimate, end. Thus, there is the ever-present possibility that the investigator may see the development of new knowledge as an end that takes precedence over the well-being of the subject. To the extent that this happens, the role of the subject increasingly approximates that of a means to another end. The subject is always at least in part a means and, in extreme cases, is entirely a means and not an end. Thus, the subject can almost never confidently delegate decision-making authority to an investigator.

Boundaries of the considerations

This paper will begin with a discussion based upon a literal interpretation of the minimum charge to the Commission. That is, there will first be a consideration of the boundary problems that arise in the course of the activities of those individuals who are licensed to conduct the "accepted and routine practice of medicine". These individuals are physicians (including psychiatrists); an exploration of their activities will reveal most of the boundaries between both biomedical and behavioral research on one hand and the accepted and routine practice of medicine on the other. However, it is acknowledged at the outset, that there are many other types of health care professionals; their activities

will be discussed later. The concentration on the activities of physicians at the outset may, to a large extent, be considered paradigmatic.

There will also be a discussion of boundary problems that may arise in manipulations of the health delivery system itself.

Other topics that will be covered include the following: There will be a discussion of some of the special sorts of problems that arise when research is conducted within the health delivery system by individuals who are not health care professionals. Further, there will be a discussion of the boundary problems created by introduction of new sorts of health "professionals" into the health delivery system. There will be a discussion of research that has no legitimate recognizable boundary with the accepted and routine practice of medicine. Specifically, this discussion will include some behavioral research and most social science. It will be demonstrated that the conceptual models used to distinguish research from practice in the medical realm may be applied to a limited extent to considerations of boundaries between the research and "practice" activities of social scientists. Finally, there will be a statement with little discussion that the conceptual models used to distinguish the boundaries between research and practice in biomedical and behavioral research might be applied fruitfully to considerations of analogous activities conducted in education and in welfare.

Conceptual models

There are two traditional models for distinguishing research from practice. The tradition of the professional (physician-investigator)--particularly the professional acting as an individual--is to distinguish research from practice on the basis of intent (of the professional). The second traditional system of classification is that generally practiced by groups (ranging from Peer Groups to

Regulatory Agencies). Groups make the distinction on the basis of acceptance or approval (by the group). It should be understood at the outset that--although these two systems of classification constantly interplay with each other--for purposes of discussion it is convenient to attempt to dissect them apart. There will first be an exploration of the utility of distinguishing research from practice on the basis of intent. This will be followed by a discussion of the devices of acceptance and approval. An attempt will be made to explore the tensions and conflicts created by the coexistence of these two models.

Boundaries defined by intent

Using intent as the taxonomic device, the activities of physicians may be defined as follows. If a physician proceeds in his interaction with a patient to bring what he considers to be the best available technique and technology to bear on the problems of that patient with the intent of doing the most possible good for that patient, this may be considered the pure practice of medicine. By contrast, if a physician interacts with an individual with the intent of developing new knowledge (not primarily for the benefit of that individual), this activity may be classified as research. The parenthetical clause in the preceding statement is meant to accommodate the understanding that diagnostic testing--which may or may not be done with research intent--develops new knowledge; if the purpose of the new knowledge is to benefit the individual directly, the activity is classified as practice, not research. In a broader context research (involving humans) may be defined as follows:

Research (involving humans) is any manipulation, observation, or other study of a human being--or of anything related to that human being that might

subsequently result in manipulation of that human being--done with the intent of developing new knowledge and which differs in any way from customary medical (or other professional) practice. Research need not be interactive; eg, observations of humans through a one-way glass, by tape-recording their conversations with each other, or by examining their records may--but need not necessarily--be classified as research.

Research may usually be identified by virtue of the fact that is conducted according to a plan. The plan (protocol) will usually indicate the intent (purpose) of the planner in conducting the activity. However, even if a plan does not exist, activities that might be considered research (as defined in the preceding paragraphs): 1) should be considered research; 2) ordinarily should be planned; and 3) should be reviewed by an IRB.

The word plan as used in the preceding paragraph means a formal plan containing a stated hypothesis, methods of procedure, and so on. It is acknowledged that almost all meaningful activity is conducted according to some sort of plan be it formal or informal. In many kinds of research--particularly in its early stages--some sort of plan may exist in the mind of the investigator who may or may not be able to state it formally. In biomedical research--particularly that involved in elucidating the "natural history" of various diseases--the initial impetus to the development of a plan most commonly is serendipitous. After an initial observation is made, the physician-investigator attempts to make similar observations on similar patients. A second common approach to developing the first findings bearing on the natural history of a disease is as follows: An investigator may develop a new test for say a new enzyme or other substance in some body fluid. He may then proceed to measure this substance rather indis-

criminally--if the intervention is relatively harmless--in the entire diseased (and sometimes normal) population available to him. Thus, when one investigator learned how to assay serotonin in body fluids he proceeded to do so in virtually every patient in the institution in which he was working. One patient had very high levels--and so on. Thus, the biochemical basis for the malignant carcinoid syndrome was discovered. As with most such research, when the final report appeared, it seemed quite rational to have deliberately set out to look for this biochemical abnormality in this disease. The research plan in this second case--owing to its similarities to Darwin's experiences--is commonly called a Voyage of the Beagle.

Similarly, social scientists may or may not begin with clearly stated hypotheses or easily articulated plans. Thus, for example, although anthropologists and ethnologists have a clear understanding of their research strategies, they ordinarily cannot state their hypotheses or provide detailed accounts of how they will apply their general strategies to their particular projects until they have begun. Similarly, even when a research plan is formally and clearly articulated at the outset by a sociologist, it may evolve dramatically and rapidly after the first few "experiments" or interviews are completed. In the early stages of social research the plan may develop heuristically as unexpected and "even more interesting" possibilities are discovered in the research environment.

Complex and simple activities

For purposes of defining problem areas, activities will be categorized as either complex or simple. A complex activity is one in which the interaction

between the physician and the individual (patient or subject) involves more than one maneuver some of which may be done with research intent and others with practice intent. A simple activity may be defined as a single maneuver the intent of which may be either research or practice.

Complex activities

First there will be a consideration of some examples of boundary problems that may arise in the conduct of complex activities. In general, the boundary problem here entails sorting out which parts of the activities are research and which are practice. Thus, if a complex activity is divided up into its component parts, one may find that of 100 simple activities only 2 or 3 are research. The reason to identify these is to enable the professional to inform the patient-subject as to which are which so that he might choose (for his own reasons) to reject some with a full awareness of the potential consequences of such rejection or acceptance. The discussion of complex activities which follows is intended to provide a basis for discussing models of informed consent in a subsequent staff paper.

1) In dealing with a patient with an unusual disease a physician may perform more diagnostic tests than are necessary to provide optimal care. The purpose of the excessive diagnostic testing might be to develop a very comprehensive description of the individual with an ultimate goal of publishing a "case report". In this situation the individual has usually contacted the physician with the expectation that he will be playing the role of patient. However, full disclosure would demand that the physician inform the individual that he is being asked to also play the role of subject. The individual should be informed that some of the proposed diagnostic tests are to be done with re-

search intent. Further, he should be informed that these tests are not necessary to provide optimal care; that refusal to accept these tests will in no way adversely prejudice the ability of the physician to provide optimal care; and that (ordinarily) the subject is not expected to pay for these tests.

2) A frequently encountered boundary problem exists when research is designed to compare the safety and/or efficacy of two "accepted" therapeutic or diagnostic modalities. While the use of either of these modalities in the context of a physician-patient relationship might not be considered experimental, a study designed to compare them is. Thus, full disclosure demands that the individual be informed that he is being invited to play (at least in part) the role of subject and what implications this may have. Among other things, during the course of the studies the subject will be subjected to more testing and closer scrutiny than would be the case if the same maneuvers were implemented as part of the usual practice of medicine. Further, the prospective subject should be informed that some practitioners of medicine may have strong feelings that one of the maneuvers being studied is clearly superior to the others and what the implications are of these strong feelings. Thus, for example, a subject may encounter in a social environment (eg, cocktail party) a physician who might express such strong feelings: What sort of lunatic talked you into taking drug B for your condition when everybody knows that drug A is superior?

Simple activities

Let us next consider some of the boundary problems that arise in considerations of simple activities. Here one is most concerned with the difficulties that might arise in providing satisfactory definitions of what constitutes

"accepted" or "best available" technique and technology. Here one is particularly concerned that the physician may use a technique convinced that it is "accepted" and "best available" while an appropriately constructed panel of peers or a regulatory agency might not agree. Some of the boundary problems in this area will be exposed through consideration of the use of drugs in the practice of medicine. It will also demonstrate that our definition of practice (as distinguished from research) contains within it a boundary problem; that is, when the concept of intent comes into conflict with the concept of what constitutes accepted or best available technology.

Conflicts between intent and acceptance or approval

If a physician wishes to use a drug that does not yet have a New Drug Application (NDA) approved by the Food and Drug Administration (FDA) this is--in the view of the FDA--research no matter what the intent of the physician. The same situation obtains if a drug with an approved FDA is used for an unapproved purpose. There are at least two problems subsidiary to this which should be studied in some detail:

The first is the conflict between the existing and proposed DHEW rules and policies governing experimentation on children and pregnant women on one hand, and, on the other, the FDA requirements for proof that a drug is safe and effective within these populations. As a consequence of this conflict in regulations and policies, the vast majority of drugs contain warnings on their FDA-approved package labels that "the safe use of this drug in children or in pregnant women has not been established", or other similar caveats. Thus, one might consider most drug use in these population groups to be either uncontrolled (unethical ?) research or (potentially) illegal practice of medicine.

The second is that in the "experience" of the practicing community a drug

may become identified as the "drug of choice" in a specific situation long before this use is approved by the FDA. In some cases this "experience" is based upon anecdotal reports or hearsay evidence. In others, there may develop a substantial body of evidence appropriately accumulated, reported, and debated which seems--in the view of physicians expert in the field--to support the identification of the agent as the "drug of choice". Examples include the use of lidocaine in the treatment of some arrhythmias; the use of propranolol and diazoxide in the treatment of hypertension, and so on. FDA recognition of such uses for such drugs may lag many years behind their acceptance in the community of practitioners.

Thus, for purposes of considering drugs as either accepted or not accepted there is the FDA which helps solve some boundary problems and which may contribute to the creation of some others. There are a variety of other types of therapeutic and diagnostic modalities for which we have no standard-setting agencies. For these, for the time being, one might consider developing mechanisms to devise guidelines which will help practitioners distinguish accepted from unaccepted. By implication, it may very well be that the best mechanism would not entail development of new federal regulatory agencies. Among the areas which might be assigned high priority at this point are the following: surgery, invasive diagnostic techniques (including biopsies and catheterizations), diagnostic and therapeutic devices, radioisotopes, radiation and other physical forms of therapy, and behavioral approaches to psychotherapy.

The FDA model

Another sort of problem that arises in considering the status of simple activities is that of determining when an activity passes from the realm of research into that of "customary or best available" or "approved or accepted"

technique. Here it may be useful to explore the approach used by the FDA in relation to drugs to see how it might be applied to the other categories of simple activities mentioned in the preceding paragraph. The development of a new drug proceeds along a spectrum which contains several discontinuities. Thus, in the development of a drug, the initial testing in humans is called "Phase I". Standards are set that permit filing of a IND which, in turn, permits moving from the pre-clinical to clinical experimentation stage. Standards are further set to determine when one may proceed from Phase I to Phase II and then to Phase III. Procedures are available to allow simultaneous conduct of these phases when appropriate. Perhaps it would be appropriate to see how this sort of phasing might be used in the development of, for example, a surgical technique or a therapeutic device. In consideration of boundaries the point of discontinuity is the passage from Phase III to approval of the drug for general distribution. This is signified by filing with and approval by the FDA of a NDA. One should be concerned with both sides of the boundary. Thus, when is it dangerous (or unethical) to consider a simple activity "standard or accepted" when it has not yet been suitably tested? Alternatively, when is it inappropriate (or perhaps dangerous) to continue research on a simple activity that has already been "proved"? In the latter case, is it appropriate to deprive individuals of this technique by further testing in "controlled" studies? It should be noted that the FDA has come to terms in a responsible manner with the understanding that there are, at times, drugs which clearly should be made available to individuals with serious illnesses but which have not yet passed full criteria for issuing a NDA. Under these circumstances a limited NDA may be issued through which only physicians who are acceptable to the FDA may prescribe

the drug and under which they assume the obligation to continue to collect data on safety and efficacy in conjunction with its use.

Innovative therapy

At this point it may be useful to examine the concept of innovative therapy. Innovative therapy is a term applied to a simple activity that is ordinarily conducted by the physician with either pure practice intent or varying degrees of mixed research and practice intent. It is distinguished from accepted and standard medical practice in that it has not been sufficiently tested to meet peer group or regulatory agency standards for acceptance or approval. To return to the drug (FDA) model, innovative therapy would be those activities classified as phase II or phase III drug trials. Ordinarily, such drug trials are done with mixed intent. There is the intent of alleviating or, perhaps, curing a disease. At the same time, there is the intent to develop new knowledge in a systematic way to determine whether this drug is better (more safe or more effective) than other drugs that might be available for the same purpose. After a sufficient number of such interventions have been performed the drug may be classified as accepted in which case the word, innovative, is no longer necessary in describing its use as therapy.

In other cases innovative therapy may be conducted with pure practice intent. Thus a physician may decide to administer a drug to a patient who has a serious abnormality requiring treatment for which there is no alternative. It might be that there is no other drug or other form of treatment available for this condition. Alternatively, it might be the case that alternative therapeutic modalities have been tried and failed. Thus, the physician may proceed with pure practice intent. In some cases the physician might not perceive himself as an

investigator and might be irritated by the fact that he cannot have access to the drug without completing certain forms designed to develop in a systematic fashion the new information required to document the relative safety and/or efficacy of this drug.

The term, innovative therapy, applies to much more than drug administration. However, it is in the area of drug administration that there now exists the most highly developed regulation. Other categories of innovative therapy include surgery, invasive diagnostic techniques (including biopsies and catheterizations), diagnostic and therapeutic devices, and so on as stated earlier.

Timely removal from the market

From the opposite point of view we should be concerned with mechanisms for formally removing an activity from the category of "standard and accepted". Again, it might be appropriate to study FDA procedures in this regard. Thus we might learn of procedures they have available for surveillance of ongoing activities which allow them to discover when certain solutions for intravenous administration should be removed from the market because they are contaminated with bacteria (temporary removal) or when a drug should be partially removed from the market (have its market limited) owing to the discovery of complications not understood at the time it was approved (eg, tolbutamide and chloramphenicol). Thus, we might discover devices for timely removal from the "market" of some surgical procedures (eg, internal mammary artery implantations and thymectomies "for convenience"), use of fluoroscopy for fitting shoes, use of routine catheterizations of the urinary bladder for diagnostic purposes, and so on.

Caution about extending the FDA model

In many cases the safety and efficacy of an intervention is directly re-

lated to the personal skill and experience of the individual who is performing it. This is most conspicuously true in some sorts of surgery. Thus, for example, when a highly skilled and experienced team of cardiovascular surgeons report the results of their experience with a specific operation one cannot assume that the same safety and efficacy will be achieved by less skilled and/or experienced surgeons. This is at least equally--albeit less conspicuously--true in considerations of behavioral approaches to psychotherapy. To some extent the personal skills and experience of the physician will influence the outcome of his use of any diagnostic or therapeutic modalities. Parenthetically, it should be noted that personal skills and experience greatly influence the outcome of the use of drugs. Thus, for example, the use of methotrexate by an experienced oncologist may yield salutary effects with minimal risk while its use by many other physicians may be deadly.

Another boundary issue that might be explored involves the psychological and other intrapersonal conflicts that develop when one individual attempts to play both roles--that of physician and that of investigator--simultaneously. We doubt that we can do much to resolve these conflicts. However, the final report of the Commission should at least acknowledge its existence and its implications. Among the individuals who have published their analyses of these conflicts are W. Bean: J. Lab. Clin. Med. 39: 4, 1952. and J. Katz: Clin. Research. 21: 787, 1973.

Other health care professionals

As mentioned earlier physicians are not the only health care professionals who might be considered. The foregoing is a partial list of health care pro-

professionals whose activities involve direct interface with individuals (patients and/or subjects). The list is not comprehensive and is meant merely to illustrate the diversity with which one might deal:

Osteopaths, naturopaths, chiropractors, dentist, podiatrists, chiropodists, pharmacists, clinical psychologists, marriage counselors, psychoanalysts (non-physician), counseling psychologists, social workers, dietitians, nurses (including licensed practical nurses, registered nurses, nurse practitioners, nurse clinicians, etc), physician's assistants (types A, B, and C) (NSF classification), Medex, child health associates, orderlies, nurses aides, radiology technicians, emergency medical technicians, and ambulance drivers.

For practical purposes these individuals can be classified in two categories: 1) Free-standing practitioners and 2) those who can act only by delegated authority from an individual in the first category. Perhaps we should concentrate in our considerations on the activities of individuals in category 1 with the assumption that they can be held accountable for the activities of those individuals to whom they delegate authority (respondeat superior). However, it should be understood that there is considerable variation in the medical practice laws of various states as to who may practice in category 1 and who may practice in category 2. Currently, there is legislation pending in several states which would move some individuals from category 2 to category 1. Further, it must be understood that some individuals in category 2 may--in the context of practice--be called upon to exercise varying degrees of independent judgment. It must also be understood that most of the individuals in category 2 may have authority delegated to them by a physician or another individual in category 1 who is engaged in research as well as practice.

Thus, in considering the boundaries between research and practice the same issues arise in considerations of these individuals as discussed earlier in considerations of physicians. The specific activities that must be considered

are enlarged by adding to the list some sorts of individuals who engage in health care activities in which physicians are not ordinarily involved; eg, dentists, podiatrists, acupuncturists, etc.

New health professionals as experimental agents

Another problem one might consider is the fact that the introduction of certain types of individuals into the health delivery system may itself be considered experimental. This issue may be considered at several levels. The first is the level at which a new type of health professional is created based on the assumption that by virtue of a formal training experience this individual will prove to be safe and effective in his prescribed function. It is difficult to anticipate the future but, looking back just a few years, at which point might one have considered the introduction of family nurse practitioners and physician's assistants into health delivery systems experimental and at what point did we begin to consider them part of the "accepted and routine practice of medicine". Through reviewing these developments we might be able to formulate guidelines for considering the present and future development of new types of allied health personnel.

At another level one might consider the extent to which introduction of new health personnel who have no formal training or certification might be considered experimental. Here we are concerned with two types of problems. The first is that a physician or other category 1 individual may undertake to train any one he selects to perform part of the professional functions. Thus, an orthopedic surgeon may train someone to apply casts, assign the title of "cast-technician" and allow that individual to apply casts with or without direct supervision. Similarly, other individuals may be trained to assume major health

care responsibilities; eg, diabetic teaching aides, genetics counselors, primal-scream assistants, receptionist-history takers, and so on. A second problem is introduction into a health delivery system of an individual who has no training whatever based on the assumption that by virtue of his experience he will be able to contribute constructively to the functions of the system. Thus, for example, ex-drug addicts are introduced into drug dependency units (eg, methadone maintenance programs), spouse-surrogates are introduced into sex therapy teams, and so on.

Should we also be concerned with institutions (or individuals) that may act outside the established health delivery system but which receive referrals from within the system which are comprised of individuals of the sort described as the second problem in the preceding paragraph? For example, we might consider organizations of people who have recovered from laryngectomies (Lost Chord Clubs), colostomies (Q-T Clubs), Alcoholics Anonymous, and Parents Without Partners.

Activities of investigators who are not health care professionals

The individual subject will not ordinarily be confused when approached by an investigator who is not a health care professional (eg, a sociologist) as to whether he is being asked to play the role of patient or subject. However, there are circumstances in which the activities of investigators who are not health-care personnel may create boundary problems. Two examples are offered for purposes of illustration.

- 1) The first is the situation in which the investigator is conducting his experiments in a health delivery setting. Thus, a sociologist interviewing patients in a hospital may be perceived by the patient (subject pro tempore)

as an agent of the hospital. The patient may not understand that this part of the total activities in the hospital is not part of the "practice of medicine".

2) Researchers who are not health-care professionals may gain access to prospective subjects through interactions with (eg, review of the records of) a physician or a hospital. Thus, in this way a physiologist may contact individuals who have recovered from myocardial infarctions or a geneticist may contact individuals with epilepsy. Again, the prospective subject may misinterpret the role of the investigators as perhaps being part of the health care delivery team. Also, in this category major issues of confidentiality are raised.

Manipulations of the system

To this point the discussion has focused on the activities of individuals operating in health delivery systems. Next to be considered are the boundary problems created by manipulations of the system itself. At what point is a modification of the system considered experimental and at what point may it be considered accepted and routine practice of medicine? A partial list of modifications of the system follows: Health maintenance organizations (HMO), pre-paid group practices, innovative social service programs, multiphasic screening, computerized medical record systems, computerized approaches to diagnostic and therapeutic decision making, experimental ambulance systems (e.g., coronary care ambulances), and experimental communications networks. Just as with all other activities discussed earlier, one might also consider here the rights of the individual to know the extent to which he is a patient or a subject as well as full disclosure of options, risks, benefits, and so on.

For example, fundamental to the concept of the HMO is that for economic reasons (among others) more people will avail themselves of more health care services. Does the provision of additional services increase the likelihood of iatrogenic diseases? If so, does an ethical question arise? If an ethical question arises does it follow that it might be resolved through regulation?

One might also consider the ethical and/or regulatory implications of computerized diagnostic and therapeutic decision-making systems. The former--based upon initial inputs--may proceed to order additional diagnostic testing without "consulting" a physician. Similarly, the latter may proceed to formulate and implement therapeutic decisions without "consulting" a physician.

Considerations of the boundaries of the charge to the Commission:

The preceding pages have been concerned with explorations of the boundaries between biomedical or behavioral research involving human subjects and the accepted and routine practice of medicine. This was based upon a tentative acceptance--as a matter of convenience--of a literal interpretation of the minimum charge to the Commission as the extent of its obligation or prerogative to explore. The assumption was discussed that some may believe that the human subject of research requires more protection--more stringent safeguards of his rights and welfare--than does the patient.

An equally tenable argument may be made that all human subjects of research require more protection than do similar individuals playing alternative roles that might be available to them. At the very least, they ought to be made aware of the facts that they are being asked to play the role of research subject, what risks and benefits might accrue to them from playing this role

and that ordinarily they have the right to refuse to be subjects without adversely prejudicing their relationship to any portion of society that they value. With that objective in mind, we may now consider briefly the boundaries between the research activities and the "practices" of professionals in two additional major categories: 1) Social sciences, and 2) education and welfare.

Social sciences:

Earlier in this paper there was a brief discussion of the activities of social scientists as they were conducting their research either within or in collaboration with the health delivery system. Those sorts of activities of the social scientist present no boundary problem to the IRB. This is clearly research. The boundary problem in that case is presented to the patient. The patient may be confused about the role of the social scientist and, derivitavely, about his own. Thus, unless the patient is informed that he is being asked to assume the role of subject during the period of interaction with the social scientist, he may consider these activities part of the standard "practices" he is expected to participate in within the health delivery system.

When social scientists are performing their activities outside the health delivery system there is clearly no boundary problem between their activities and the "accepted and routine practice of medicine".

Are there any boundary problems to be considered in the activities of social scientists between their research and "practice" activities? First, it seems appropriate to state that in considering the usual activities of sociologists, anthropologists, political scientists, and so on, there is no boundary problem since they have no professional practices other than research.

However, the activities of some social scientists will present us with substantial boundary problems between their research activities and professional practices (it should be clear at this point that the scope of the word practice now is extended deliberately beyond the definition contained in the charge to the Commission). A major boundary problem might be presented by the activities of a criminologist who also either is himself a law-enforcement officer or is working in collaboration with a law-enforcement agency. Similar, though less dramatic problems might be presented through considerations of the activities of systems analysts, administrative scientists, and so on. Other sorts of boundary problems are presented by the fact that some social scientists contribute to the formation of public policy. As a consequence of their usual professional activities (doing research) they may develop knowledge that will be used to "remedy" the societal dysfunctions they have "diagnosed". Thus, in this fashion, their role might be compared to that of the physician with society as the patient-subject. Thus, perhaps in some cases, it is society that we ought to offer the opportunity to give informed consent.

The definition of research based upon intent of the professional as modified through considerations of "accepted" or "approved" provided earlier in this paper might be equally applied to considerations of the activities of social scientists: To reiterate:

Research (involving humans) is any manipulation, observation, or other study of a human being--or of anything related to that human being that might subsequently result in manipulation of that human being--done with the intent of developing new knowledge and which differs in any way from customary medical

(or other professional) practice. Research need not be interactive; eg, observations of humans through a one-way glass, by tape-recording their conversations with each other, or by examining their records may--but need not necessarily--be classified as research.

What one is most concerned with in the activities of the social scientist is that through his research activities he develops enormous power for "subsequent manipulation". In general, the most serious issues that seem to arise in protection of the subjects of research in the social sciences are of two sorts. The individual research subject may risk violations of confidentiality and privacy. The community of which the subject is a part is also put at risk, as the social scientist uses the information in his publications or as the basis of his consultative opinion leading to the formulation of public policy. A detailed analysis of the risks and benefits of social science research will be the subject of another staff paper.

Boundaries between research and practice in education and welfare:

It is of historical interest that most federal regulation concerned with protection of human subjects of research has been concentrated in the Department of Health, Education and Welfare. In fact, PL 93-348 requires of the Commission that it make recommendations to the Secretary, DHEW. Curiously, thus far almost all regulation oriented toward protection of human subjects has focused on health. There seems to be little recognition in existing legislation or regulation that considerable research involving human subjects is done in the fields of education and welfare.

Experiments in education and welfare may influence the lives of "experimental subjects" dramatically. The risks and benefits are at least as great--though not often so immediate--as those conducted in the field of health. Here, in contrast

to the social sciences, there is virtually always a problem in distinguishing between research on one hand and, on the other, accepted and routine "practices". Thus, if one wishes to consider the boundaries between research and practice in these fields one might begin with essentially the same conceptual model developed in this paper.

The Commission is aware of the problems in education and welfare but has-- for the time being--decided to consider these problems outside the "boundaries" of its charge.

ADDENDUM - September 24, 1975

Elaboration of definitions and concepts

One purpose of this addendum is to clarify the definitions of some of the words used in the paper, "The boundaries between biomedical or behavioral research and the accepted and routine practice of medicine" (July 14, 1975)--hereafter referred to as "this paper". A second purpose is to clarify and formalize some of the concepts that were developed in this paper. Special attention will be devoted to those words and concepts that provoked either controversy, misunderstanding, or both in the course of discussion of this paper at the September, 1975, meeting of the Commission.

The definitions of words used in this paper are those contained in Webster's Third New International Dictionary. The words that presented the greatest problems are: research, experiment, practice, intent, and innovative. Examination of their definitions in the dictionary will reveal that several have many definitions and when used in various contexts may have differing connotations. An attempt has been made throughout this paper to adhere to dictionary definitions so as to avoid development of unnecessary neologisms.

Dictionary definitions

Research: The most important definition of research used in this paper is that provided for the word when used as a noun. "2a: Studious inquiry or examination; especially: critical and exhaustive investigation

or experimentation having for its aim the discovery of new facts and their correct interpretation, the revision of accepted conclusions, theories, or laws in the light of newly discovered facts, or the practical applications of such new or revised conclusions, theories, or laws."

Experiment: Noun. "1a: A test or trial; b(1): A tentative procedure or policy--especially: One adopted in uncertainty as to whether it will answer the desired purpose or bring about the desired result...c: An act or operation carried out under conditions determined by the experimenter (as in a laboratory) in order to discover some unknown principle or effect or to test, establish, or illustrate some suggested or known truth." As an intransitive verb: "To engage in experimentation."

Experimental: Adjective. "1: Of, relating to, or based on experience. 2a: Founded on, derived from, or discovered by experiment (the heart of the experimental method is the direct control of the thing studied)."

Practice. Noun. "1b: Actual performance or application of knowledge as distinguished from mere possession of knowledge: Performance or application habitually engaged in; usually: repeated or customary action. c(1): The usual mode or method of doing something (the practice is to use a local anesthetic)." As an intransitive verb: "3: To exercise or pursue an employment or profession (as medicine or law) actively. Synonyms: Act, operate, proceed."

Intent: Noun: "1a(3): The state of mind or mental attitude with which an act is done: volition--b: An end or object proposed: aim." As an adjective: "2b: Having the mind or will concentrated on some end or purpose: determined, resolved, bent."

Innovative: Adjective: "Characterized by, tending to, or introducing innovations."

Innovation. Noun. "1: The act or an instance of innovating: the introduction of something new; 2: Something that deviates from established doctrine or practice: Something that differs from existing forms."

Discussion

Much of the discussion will focus on the necessity to use intent as a taxonomic device to distinguish research from practice. This will have the effect of focusing further discussion on this apparently controversial term. However, on page 5 it is pointed out that intent is only one device. It is the one that is traditionally used by the individual professional; this will be discussed further below. The second system of classification is a social system; ie, that system generally employed by groups. These groups--such as Peer Review Groups, Institutional Review Boards, and Regulatory Agencies make their distinctions on the basis of whether an activity or procedure meets certain criteria of acceptance or approval. Some of these groups also have the authority to either not accept or disapprove. Thus, a group may first classify an activity as either research or practice and then further proceed to say it is either bad research or bad practice and therefore either unacceptable or unapproved.

These two systems of classification are almost never totally dissociated in the conduct of activities in the real world. Thus, even when intent is used as the taxonomic device (page 6) the definition of practice contains the concept that the physician uses "...what he considers to be the best available technique and technology...". This, then reflects the judgment of the individual professional as to what is customary, standard, accepted,

approved, and so on. Subsequently, throughout the paper, examples are given of situations in which the judgment of the individual may conflict with that of a Peer Group or Regulatory Agency. It is in these situations that some of the more serious boundary disputes are enacted.

Why is the device of intent necessary?

Examination of the dictionary definition of research reveals that a key word in the definition is "aim". In the dictionary this same word is equated with one important definition of intent. The dictionary definition of practice is not particularly helpful in these considerations. It does seem to support what has been described previously as the social or group approach to defining practice. Thus, when practice is defined as a "repeated or customary action" it seems to relate to the standards of a community of professionals. Some support for using the device of intent to identify practice may be found in the Oath of Hippocrates: "I will follow that system of regimen which, according to my ability and judgment, I consider for the benefit of my patients..." The restatement of this Oath at Geneva in 1948 includes the following statement: "The health and life of my patient will be my first consideration." Thus, it seems appropriate to equate such words as contained in these avowed purposes of the medical profession with the dictionary definition of intent.

Admittedly, there is no way to measure or evaluate intent unless it is expressed clearly to the individual or group having the responsibility to evaluate or measure it. Ordinarily, this will require that a formal plan (protocol) be developed as discussed on page 7. However, some further support for using intent as a classifying device may be found by reexamining

the purposes of this paper (pages 1-3). In order to respond to any of these purposes it will be necessary to have intent described as part of a formal plan. Clearly, most activities of health care professionals are not conducted according to formal plans. At the moment a decision is made to proceed with an activity--be it complex or simple--the "plan", if any first exists only in the mind of the professional. Before the plan exists the professional ordinarily first perceives his intent. His intent may be to practice or it may be to conduct research or it may be to accomplish both intents simultaneously. Existing customs and regulations demand that if his intent is research it should ordinarily be expressed formally as a protocol and reviewed by an IRB before he proceeds. Further, in the negotiations between the professional and the individual (patient or subject) the intent of the professional should be made clear. The professional should either agree (often tacitly) to the request of the individual to establish a physician-patient relationship or he should invite the individual to play the role of subject either in addition to or in place of the role of patient. Part of informing for purposes of securing consent in the research context is to advise the prospective subject that--to some extent at least--the purpose (intent) of the activity will be to develop new knowledge.

The definition of research provided in this paper is designed, in part, for the benefit of the professional who will wish to distinguish which of his activities may be viewed (by others) as research. He may be advised that, at some moment when he is considering performing some activity, he can consider whether his intent is in part or in whole research as contrasted with practice.

In that case he may be advised further to express his intent in the form of a protocol and have it reviewed by an IRB. He may also be advised to conduct his consent negotiations with the prospective subject so as to make clear his intent to that individual.

Definition of research

The definition of research abstracted from the dictionary is a perfectly adequate description of what "good" research ought to be in general. However, for the purposes of these considerations the dictionary definition is not adequate to define or consider the boundaries between research and practice. It is not adequate in at least two respects. Firstly, much of what all will agree are part of the customary "practice" activities of physicians fulfills the requirements of the dictionary definition of research. Thus, for example, most diagnostic activity might technically be classified as research. A powerful argument has been developed by Francis D. Moore (Daedalus, Spring, 1969, cited in detail below) that even much therapeutic activity performed by a physician might be considered "experimental". In this regard the dictionary definition is too broad to meet the purposes described on pages 1-3.

On the other hand, the dictionary definition may be considered too narrow to meet these same purposes. The dictionary definition as mentioned earlier is a good general definition of "good" research. However, a strict interpretation of this definition would exclude "bad" (poorly designed) research. Certainly, one would wish to have such activities reviewed by an IRB.

Now let us reexamine the definition of research presented on pages 6-7. The basic operational elements of the dictionary definition have been retained.

What has been removed are the words such as "critical", "exhaustive", and so on, that have connotations of quality. The words "investigation" and "experimentation" have been replaced with "manipulation observation, or other study". As may be seen in the dictionary definitions of the words experiment and experimental, these words--when used to establish a subset of the universe of activities which may be classified as research--have connotations of intervention, manipulation, or control over the thing or situation being studied. The word manipulation is meant to incorporate most research activities that can be defined as experimentation. It would be perfectly appropriate to replace the word manipulation with experimentation if it is clearly specified which definitions of this word are intended. The first two definitions of experiment as a noun would incorporate the concept of innovative therapy (to be discussed subsequently). It is intended in this definition to incorporate innovative therapy as a form of research.

The purpose of the wording "--or of anything related to that human being that might subsequently result in manipulation of that human being--" is to recognize that some research that is not performed directly on human subjects may put these subjects at risk. Thus, as discussed elsewhere in this paper, examination of medical records may put humans at risk; it may, for example, lead to invasions of privacy. This concept is spelled out in greater detail in the second sentence of the definition.

Also retained from the dictionary definition is the concept of "aim".

Here it is expressed as intent. The reasons for this have been described in detail.

The final concept retained from the dictionary definition is that "of developing new knowledge". However, for purposes stated earlier, this brief phrase has been stripped of those descriptors calling for quality. Also, to distinguish this from customary diagnostic and some therapeutic activities the words have been inserted: "and which differs in any way from customary medical (or other professional) practice".

Various suggestions were made by several Commissioners to add additional attributes to the definition of research. Thus, for example, it was suggested that research might be an activity so designed as to lend itself to statistical analysis; be replicable, and so on. For the same reasons the decision was made to remove from the dictionary definition terminology having qualitative connotations, I should like to avoid adding these attributes. Additionally, some of these attributes would exclude some sorts of activities discussed on pages 7-8 in the two paragraphs concerned with problems in developing formal protocols.

It was suggested further that research might be distinguished from practice by virtue of examination of the fiduciary relationship or the social structure of the relationship between the professional and the individual (patient or subject). Similarly, the reward system--whether payment is made to the individual for participating in the activity--might be considered a classifying device. I suggest that these are not classifying devices; they are rather phenomena that occur as a consequence of having made the classification.

Innovative therapy reexamined

The development of innovative therapy as a distinct category of the activities of health care professionals was established firmly by Dr. Francis D. Moore in his article entitled "Therapeutic Innovation: Ethical Boundaries in the Initial Clinical Trials of New Drugs and Surgical Procedures" (Daedalus, Spring 1969). The title of this essay implies that Dr. Moore was concerned only with therapy. However, he clearly calls attention to the fact that this classification includes prophylaxis (eg, oral contraceptives and vaccination are used as two of his major examples) and "...the initial employment of untrained personnel in the care of patients." The class he develops is somewhat analogous to that defined as "therapeutic research" (Research on the Fetus; Report and Recommendations, page 6) including not only treatment but also prophylactic and diagnostic methods. Thus, perhaps a better name for this class of activities might be Innovative Practice.

In defining this class of activities it seems appropriate to use the definitions of innovative and innovation found in the dictionary. In this case it should be made clear that "the introduction of something new" does not only mean introducing a modality that is new in kind. When an old modality is used for a new purpose this may be classified as innovation. For example, aspirin, which has been used for many years to provide symptomatic relief for pain, inflammation, and fever, has recently begun to be used as an anticoagulant. Similarly, thyroid ablation by either surgical removal or administration of radioactive iodine was introduced for treatment of hyperthyroidism. Performing the same procedure for purposes of relieving angina pectoris must be considered an innovation. Additionally, using a higher

or lower dose either of a drug or of radiation administered for therapeutic or diagnostic purposes must also be considered innovative.

It is proposed that innovative therapy (or practice) be developed as a distinct subset of the activities of physicians and other health care practitioners. It may be distinguished from practice (as defined in this paper) by virtue of its newness. The attributes of the activity which may be new include any or all of the following: It may be an entirely new modality or it may be an old modality used either for a new purpose, in a new dose schedule, or in combination with other new or old modalities. Innovative therapy (or practice) may be distinguished from other sorts of research in that there is some scientific basis for predicting that some direct health benefit will accrue to the subject. Thus, innovative therapy most closely approximates the category of "therapeutic research" as previously defined by the Commission. In general, innovative therapy should be conducted and reviewed as if it were research. Some possible exceptions will be explored below. Operationally, the definition of innovative therapy should accommodate the knowledge that many aspects of the practice of medicine can be stated in only general terms; eg, how in general one might diagnose or treat a category of patients. As one examines most diagnostic and many therapeutic activities conducted on a particular patient, a rigorous analysis of the activities will indicate that something that someone might call innovative has been performed. Thus, the physician commonly "experiments" with various doses of various drugs to find the combination most suited to the particular patient. The surgeon and the psychotherapist also

commonly deviate from textbook descriptions of their particular types of therapy in order to be responsive to the needs of the particular patient. Therefore, the definition of innovative therapy--for purposes stated on pages 1-3--should assume that the adjective substantive will be applied to the word innovation.

In the original draft of this paper it was proposed that areas of innovative therapy that should be scrutinized particularly carefully include the following: surgery, invasive diagnostic techniques (including biopsies and catheterizations), diagnostic and therapeutic devices, radioisotopes, radiation and other physical forms of therapy, behavioral approaches to psychotherapy, and the development of new health professionals. There should be some sort of group mechanism to establish standards of acceptance and approval for these categories of activities. Activities in many of these categories are being defined by the individual professional as either research or practice purely on the basis of his intent. What is needed is some sort of group to apply the classification devices of acceptance, approval, safety, and efficacy. An appeal for the development of such standards for behavioral approaches to psychotherapy has recently been transmitted to the Commission in a letter from Dr. Daniel X. Freedman to Commissioner Brady (July 3, 1975).

In the initial draft of this paper it was proposed that--to the extent possible--the FDA model designed to review the use of drugs be applied to these other categories. Parenthetically, it is re-emphasized that this is not necessarily to be construed as a requirement for new federal regulatory agencies.

The FDA model--as a social device for developing standards of accepted

or approved (or safe and effective)--was discussed in this paper only to the extent that it assists in defining the boundaries between research and practice. However, it should be made clear that this model has additional features which would be responsive to the wishes of the Commission as expressed at the September, 1975, meeting. The FDA model provides criteria not only for defining which of the activities under its purview are research and which are practice, it also provides criteria for determining which of these activities are acceptable and which are not acceptable. A strong concern expressed by some Commissioners is that some activities performed as "therapeutic innovations" are considered by some to be practice activities. Therefore, they may not have applied to them the social device of acceptance or approval. Thus, "bad" therapeutic innovations may be introduced and may cause inappropriate harm. In general, if for purposes of review, innovative therapy (practice) is classified as research and reviewed by IRBs--and when necessary, groups constructed to perform the functions of the FDA--the likelihood of introduction of "bad" innovative practices should be minimized.

The FDA model demands that certain criteria be met before a potential therapeutic innovation might even be considered an acceptable research activity. Thus, to the extent possible, the potential innovation must be studied in appropriate animals. After appropriate animal and other pre-clinical testing has been accomplished it may be deemed appropriate to proceed with phase I clinical studies. This is the point at which the innovation has been classified as acceptable research on humans. Phase I clinical

studies on a drug are not truly innovative therapy. This is because the intent of phase I studies is not to bring direct benefit to anyone; rather it is to determine the toxicity (or relative safety) of the drug. In most cases the subjects selected for phase I studies are normal. Innovative therapy ordinarily begins with phase II in which--in a very controlled setting--the drugs are first administered to individuals having the disease which the drug is designed to treat (target population).

Let us now examine this part of the FDA model to see how it might be applied to other categories of innovative therapies (practices). First, it should be recognized that all concerned have agreed that in some drug studies phase I should be omitted. This is particularly true when the drug to be studied is one which on the basis of animal testing is predicted to have serious toxicity and which is designed to treat a very serious disorder. Thus, for example, some highly toxic drugs are designed to treat patients with cancer. Customarily, clinical trials of these drugs begin in phase II; ie, the first humans to receive these drugs after appropriate animal testing are individuals with cancer in whom other forms of therapy have been tried and have failed. It would be clearly inappropriate to expose normal subjects to such high toxicities without the at least hoped for benefit of relief from some serious disease.

Preclinical testing leading to the equivalent of a INDA clearly can be accomplished with therapeutic innovations in many forms of surgery, invasive diagnostic techniques (including biopsies and catheterizations), diagnostic and therapeutic devices, and so on. Of the categories specified for

which the social device of acceptance or approval should be developed, the only one in which preclinical testing may not be useful is behavioral approaches to psychotherapy. Just as with drugs, preclinical testing should allow us to predict to varying extents the safety and efficacy of these other types of activities. There will be clear cases in which appropriate animal models do not exist. However, this should be no more limiting in most other categories than it now is with drugs.

Phase I studies as described for drugs would be clearly inappropriate for testing of most other innovative therapies. As Dr. Moore has pointed out, it is quite impossible to begin with small doses of surgery and gradually build up until a toxic dose is found. However, there may be some therapeutic innovations that we might wish to first test in normal subjects. Thus, for example, in the development of new health professionals they might first "practice" on normal volunteers. Similarly, in diagnostic radiology, an important function of an innovative technique might be to distinguish various types of abnormality from normal. In order to do this it is necessary to perform the new diagnostic radiologic technique on normal humans. This presents little problem when the new technique involves producing a roentgenogram in a new way delivering a low dose of radiation. On the other hand, problems are presented when innovative diagnostic radiology is combined with invasive (eg, catheterization) techniques or when high doses of radiation must be administered.

In some other forms of innovative practices normal humans may be the only intended target population. This is particularly true in considerations of innovative prophylactic techniques such as immunization to various diseases

transmitted by viruses and microorganisms and in pharmacologic or surgical approaches to contraception.

In considering the FDA model as it might be applied to innovative therapies in general the most important phases in the development are II and III. Phase II is begun after appropriate preliminary studies have indicated that the hoped for benefit might be achieved and that the risks of harm are likely to be outweighed by the probability and magnitude of the hoped for benefit. In cases where it is impossible to make such determinations or to develop such expectations based upon prior preclinical and phase I testing there should be at least some theoretical framework within which the innovation is first performed. It should be possible to state formally within the context of some theoretical framework--or, perhaps, by analogy--that the criteria for beginning phase II have been met. As phase II is begun, the innovation is performed in a stringently controlled environment using a small number of subjects derived from the target population. After sufficient data are accumulated to show promise of safety and efficacy in this small target population, the activities proceed to be conducted according to phase III standards. In this phase a much larger population is exposed under much less controlled conditions gradually approaching those under which the innovation might be used in practice.

The basis for developing innovative therapies in this fashion is as follows: Very early in phase II the power to predict either the risks or benefits of the innovation are minimal. With continuing experience and repetitions of the innovation the power to predict both harms and benefits increases progressively. The process of increasing the power to predict is enhanced if the innovation is performed in a setting which most closely ap-

proximates the research (dictionary definition) setting. Thus, as one proceeds to attempt to benefit patients--in accord with the definition of practice as defined in this paper--one should ordinarily also be conducting research.

In general, individuals conducting innovative therapy should be considered both health practitioners and investigators. The innovative therapies should, in general, be conducted according to the highest standards of the relevant scientific discipline. In that way it might be possible to avoid the introduction of therapeutic innovations which have not been tested adequately and which informally pass into the realm of "usual and customary". It is preferable to conduct formal and controlled experiments during the process of innovation rather than after the innovation has become firmly established as customary practice.

Once the innovation has become established as customary practice it is much more difficult to study it in a systematic way to determine its safety and efficacy. For example, in 1966, the National Academy of Sciences, initiated--under contract from the FDA--a review of drugs introduced into the market between 1938 and 1962. The purpose of this review was to determine whether each of these drugs was effective for the indications designated by their manufacturers. Their report (Drug Efficacy Study, Final Report to the Commissioner of Food and Drugs, from the Division of Medical Sciences, National Research Council, NAS, Washington, D.C., 1969) categorized drugs as effective, effective but, probably effective, possibly effective and ineffective; it further made recommendations as to how data might be developed that would lead to reclassification from intermediate categories to either effective or

ineffective. Now, 6 years later, the FDA is still proceeding with the implementation of these recommendations. Many drugs originally placed in intermediate categories remain on the market without having had the deficiencies in documentation of their efficacy supplied.

If all innovative practices were studied systematically during the process of innovation it is likely that fewer "bad" innovations would become firmly established as customary practice. Had this been the usual approach to innovation in the past, many individuals might have been spared subsequently abandoned dangerous surgical procedures ranging from routine tonsillectomies, to a variety of surgical procedures for treatment of coronary artery disease, and to prophylactic portal-caval shunts for the treatment of esophageal varices (a complication of cirrhosis of the liver).

In exceptional circumstances, an innovative therapy might be used in a pure practice context. Thus, for example, a patient with a life-threatening illness requiring emergency treatment may be delivered to a hospital that is not prepared to perform the innovative treatment in conjunction with those measurements that would be designed to contribute to the general fund of information on its safety or efficacy. Further, it may be that no alternative therapy is available for this individual. In such situations it seems appropriate to proceed with the new form of therapy as if it were "standard or accepted". It further seems appropriate to proceed without having consulted an IRB or any group that might impose group judgment on the activities of the professional. However, in such situations, the physician (or other health care professional) should be aware that subsequently he is likely to be held accountable for his actions by some appropriate group. In cases of

this sort, the group is likely to be the hospital board. Perhaps in the future it will be the IRB.

Conclusions

The definition of research presented in the first draft of this paper should be retained. However, it should be pointed out that--for reasons described--it departs to some extent from the definition provided by the dictionary. Perhaps the Commission will wish to state in its recommendations that this is not a definition of research; rather, this is a definition of how a subset of the universe of activities of health care professionals may be distinguished from practice. The purposes of making such a distinction are at least those described on pages 1-3 of this (the original) paper. It would be appropriate--should the Commission wish--to replace the word, manipulation (the first time it appears in the definition) with the word, experimentation.

For practical purposes, the definition of research as provided in this paper, includes innovative therapy (or innovative practice). This means that any innovative practice in which the deviation from customary practice is substantive should be conducted so that it most closely approximates the standards of good research (as defined by the relevant scientific discipline) without obstructing the intent to bring direct health benefit to the patient-subject. It further means that the proposed innovative activity should be reviewed by an IRB, that the consent negotiation indicate that the activity is being performed with--at least in part--research intent, and so on.

The primary purpose of this paper was to consider the boundaries between biomedical or behavioral research and the accepted and routine practice of

medicine. A reexamination of the paper indicates that the boundary that presents the greatest problem is, in general, the boundary between accepted and routine practice on one hand, and, on the other, innovative therapy (or practices). The boundaries between practice and other types of research-- eg, what the Commission has previously defined as "nontherapeutic research" will ordinarily present no problem whatever. The definition of research provided in the dictionary can be applied without modification to almost all "nontherapeutic research".

2

THE ROLE OF ASSESSMENT OF RISK BENEFIT CRITERIA
IN THE DETERMINATION OF THE APPROPRIATENESS OF
RESEARCH INVOLVING HUMAN SUBJECTS

Robert J. Levine, M.D.

October 27, 1975

The Commission is charged with the responsibility to consider, among other things: "The role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects."

In the charge to the Commission a key word appears to be "role". The charge does not seem to call for a comprehensive analysis of risks or benefits but rather for an evaluation of what the role* of such analysis or assessment is or ought to be in the determination of the appropriateness* of research. Let us begin with the assumption that we do not now know what the role of such assessment is. This should be discovered through the empirical studies of Institutional Review Boards (IRBs) that are now being conducted by the Commission. This paper will be more concerned with what the role ought to be.

In order to provide a basis for discussion of the role of assessment of risk-benefit criteria it will first be necessary to agree upon what phenomena might be considered risks and what might be considered benefits. Thus, this paper will begin with a general discussion first of risks and then of benefits both to individual research subjects and to society (and various sub-sets thereof). There will be no attempt to mention all conceivable risks and benefits. Rather, there will be a classification of risks and benefits to demonstrate in general what is meant when the words are used to describe or predict the consequences of research.

After risks and benefits have been classified and discussed we shall turn to the primary focus of this paper; ie, a consideration of the role of assessment of risk benefit criteria...Implicit in the charge to consider the role of assessment of risk benefit criteria is the suggestion that there

*These words, as used in this paper, are defined in the section entitled "Definitions of role and appropriateness".

might be other criteria which are or should be used to determine the appropriateness of research involving human subjects; this suggestion will also be explored.

Many literature citations on risks and benefits are contained in: Katz, J.: Experimentation with Human Beings, Russell Sage Foundation, New York, 1972. As a matter of convenience, this reference will be cited as often as possible; such citations will appear as (Katz, pp. 10-12). Those who wish to see the primary sources will find them cited on those pages. However, since some novel examples have developed since 1972, it will be necessary to cite other sources; whenever possible a survey article in a readily available publication will be used.

Definitions of risk and benefit

The definitions of risk and benefit to be used in this paper are those contained in Webster's New International Dictionary, Second Edition. Since not all of the definitions contained in that dictionary are germane to the present discussion, the following is a clarification of which definitions are to be used.

Risk, noun: 1. Hazard; danger; peril; exposure to loss, injury, disadvantage, or destruction; as, mountain climbing involves great risks; risk of assassination.

2. (This definition is not to be used). In forest-protection usage, any agency that may cause a fire.

3. Insurance. a) The chance of loss or the perils to the subject matter of the insurance covered by the contract; also, the degree of probability of such loss. b) Short for the amount of risk, that is, the amount which the

company may lose. c) (Not to be used.) Loosely, a person or thing considered with reference to the risk involved in placing insurance upon him or it.

The word risk will also be used as a transitive verb. 1. To expose to risk, hazard, or peril; venture; hazard; as, to risk one's person or reputation.

2. To incur the risk or danger of; to venture upon (something involving risk); as, to risk a battle.

In this paper, risk will not be used as an intransitive verb.

Benefit, noun: 1. (This is an obsolete definition which will not be used). A good deed.

2. (This definition has questionable application to the present discussion; in general the word as used in this paper is not intended to have this definition.) Act of kindness; favor conferred; gift; benefaction.

3. Whatever promotes welfare; advantage; profit.

4. Specif.: a) Pecuniary advantage or profit.

5, 6 and 7 are either obsolete or not germane to these considerations; they will not be used.

8. Pecuniary help in time of sickness, old age, loss of employment, or the like.

Synonyms: Help, service, use, avail. Antonym: Injury.

Benefit will also be used as a verb. transitive: To be beneficial to; to do good to; to advance; improve; profit. ^{intransitive.} To gain advantage; to receive benefit; to profit; as, he will benefit by the change.

The terms risk and benefit as defined in the dictionary are not clearly parallel constructions. Risk, whether used as a noun or a verb, is a term that

deals with prediction of some future occurrence of harm. Risk may be expressed in terms of probability that a certain harm will occur. The harm or injury itself may be evaluated quantitatively; eg, it may be described as either a large or a small harm. The meaning of such constructions as "small risk" thus becomes unclear; this might mean a small probability of an unspecified amount of harm or an unspecified probability of a small amount of harm.

By contrast, the term benefit has no intrinsic connotations of prediction or probability. Benefit, whether used as a noun or a verb, denotes something of value that can be supplied upon demand or as one wishes. It is of interest that the antonym of benefit, injury, is the phenomenon, the probability of which we are stating when we discuss risk. It should be made clear at the outset that while discussing benefits--particularly direct health benefits of research--one is ordinarily discussing probability of hoped-for benefits.

It was observed by the Commission (transcript, September 13, 1975), that the uses of the words risk and benefit, as defined in this section, are different from those used in common parlance; this is intended. The author shares the view that the common use of such shorthand expressions as "risk-benefit criteria" or "risk-benefit analysis" has unfortunate practical consequences. The scholar concerned with exact meanings of words finds the expression "risk-benefit" offensive because it is dysmorphic; it seems to equate, or make parallel things which really are not (supra). Even more perilous is the effect such constructions may have on the thought processes of decision-makers. Thus, it is possible that decision makers at all levels (eg, Congressmen, Commissioners, IRB members, investigators, prospective subjects) may--by virtue of frequent exposure to the

expression "risk-benefit"--come to think that these are, in fact, parallel constructions. As they are determining the appropriateness of any particular research proposal they may think that risks can be expressed in the same terms (eg, units of measurement) as benefits and be misled to ill-founded decisions. To avoid this problem, it is suggested that all communications describing risks and benefits to individuals or groups having the responsibility to make decisions be described in language that conveys the true meaning of what is to be assessed and, perhaps, balanced.

There will be found throughout this paper various attempts to maintain parallel constructions. Thus, for example, risk is parallel to probability of benefit and benefit is parallel to risk manifested as harm.

RISKS

In this section there will be a consideration of the various sorts of risks that are assumed by human beings as a consequence of research. It should be understood at the outset that what is being categorized is risk--not research. The categories in which risks will be considered are physical, psychological, social, legal, and economic. These are the risks of research generally. Research on human subjects has previously been classified (boundaries paper) as biomedical, behavioral, and social. Some examples will be provided in this paper of risks to human beings that may occur as a consequence of research not done on human beings; eg, basic laboratory research. Some types of research present risks that are peculiar to that category of research. These will be mentioned when appropriate. Otherwise it will be assumed that the reader understands that certain sorts of research are much more likely than others to present certain categories of risk; eg, interventive biomedical research is

likely to entail physical risk while social research is not.

Risks to subjects

Physical risks

In some types of experimentation with human subjects the physical risks will be obvious. Thus, when a well-known technique is used with research intent it should, in general, be relatively easy to provide a totally adequate description of physical risk. A fully adequate description would include a statement of the likelihood of its occurrence, its severity, its duration after the research maneuver is discontinued, its reversibility, measures that can be employed for its early detection, methods that can be employed to treat or correct it, and so on (see section on adequate description of risks and benefits). Thus, when coronary sinus catheterization (a standard diagnostic maneuver) is done with research intent, all of the information called for in the preceding sentence can be provided.

In some situations the physical risk assumed by the subject is somewhat less obvious. Thus, for example, when a relatively new drug is used experimentally in the treatment of a disease for which there exist other proved drugs, one of the risks involved is that for the duration of the study the subject will be deprived of the benefit of the proved drug. It may well be that the experimental drug will prove to be superior to the proved drug; however, this cannot be assumed during the course of the experiment. Further, the adverse effects of the experimental drug may prove to be either more or less severe

than those of the proved drug. An extension of this problem is seen when therapy is withheld either for purposes of doing placebo-controlled studies or for the purpose of making physiologic measurements in patients with various diseases without the influence of drugs.

Another form of subtle physical risk is that seen in "double blind" studies. A subject in a "double-blind" study may become ill and require the emergency services of a physician who is unfamiliar with the study. It may be necessary for that physician to implement treatment promptly. It may be impossible to implement rational treatment without knowledge of what drugs the subject (now become patient) is taking. Thus mechanisms must be developed to assure immediate access to the codes for "double-blind" studies in emergency situations. In fact, such mechanisms have been developed and are functioning well. A detailed account of these will be provided should the Commission wish it.

The physical risks of some forms of experimentation are totally unknown. This is the case in most "phase-1" drug studies as well as in most other studies when an intervention is performed on human beings for the first time. Ordinarily in these cases there is ^{some} background of experience derived from experiments on animals which will help predict with varying degrees of confidence what the risks might be to humans. However, it must be clearly understood that one never knows what the adverse (or for that matter, beneficial) effects of any intervention in humans will be until the intervention has been adequately tested in humans. This statement may be extended further: The effects of any intervention in any particular class of humans cannot be known with certainty until that intervention has been adequately tested in that particular class of humans. For example, as the Commission has previously

considered in great detail, some drugs that are acceptably safe for adult males produce severe adverse effects when they are administered to pregnant women or infants. In fact, it is through adverse reactions to various interventions that we have discovered that some "classes" of humans exist. Thus it was through thorough investigation of certain individuals with drug-induced hemolytic anemia that we learned of the existence of glucose 6-phosphate dehydrogenase deficiency. Similarly, through adverse reactions to succinylcholine we learned of plasma cholinesterase deficiency. These 2 conditions are genetically determined enzyme deficiency states that have no clinical manifestations unless the afflicted individual is exposed to some drug or other chemical which precipitates reactions peculiar to these individuals. The reactions may be severe; in fact, at times, lethal.

In some other cases physical risks might be totally unknown while an intervention is in its experimental phases owing to long periods of latency between the intervention and the development of the adverse effect. For example, the suggestion that reserpine used in the treatment of hypertension might increase substantially the risk of women to develop breast cancer was first made approximately 20 years after this drug had become an "accepted" (non-experimental) form of treatment for hypertension.

Some physical risks may be derivative. For example, inoculation of children with rubella may result in inadvertent transmission of that virus to a pregnant relative, neighbor or teacher. This, in turn, if the pregnancy is in the first trimester, could result in the birth of a baby with serious deformities.

Psychological Risks

It is important to distinguish between the psychological risks of research in general and risks that are peculiar to psychological or other be-

havioral research.

Let us first consider some of the risks that are more or less peculiar to behavioral research. First, it should be acknowledged that much research directed at the patient (subject) with a behavioral disorder carries with it risks that have been classified as physical, social, legal, and economic. Thus, for example, early trials of electric shock therapy were associated with a high incidence of serious injuries to the spine. Many of the drugs used to treat psychiatric disorders present to the subject the risk of physical harm; conspicuous examples include severe liver degeneration--often fatal--as a consequence of administration of iproniazid (an antidepressant no longer in use) to depressed persons and obstructive jaundice in association with phenothiazine (a class of major tranquilizers) administration. Other risks have their parallels with those described for physical risks but which may be manifest as psychological risks in the context of research directed at psychiatric patients. These include the consequences of withholding of "proved" therapy in order to test experimental therapy, placebo-controlled studies, and "double-blind" studies. It is even more difficult in this category to predict either the adverse or beneficial effects of previously untested interventions owing to the fact that many human psychological disorders have no appropriate animal analogs.

Some special problems are presented by psychological research in which one knowingly invades the psychologic integrity of the subject. Thus, for example, in the well publicized studies of Milgram (Katz, pp. 358-365), designed to test some conditions of obedience and disobedience to authority, normal volunteers were deliberately deceived. They were led to believe that at the command of the investigator they were inflicting pain upon third persons.

In some cases they were led to believe that the pain they were inflicting by way of electric shock was unbearable. Some of the subjects experienced extreme anxiety. Some were startled to learn the brutality of which they were capable; some detached themselves from a sense of responsibility by persuading themselves that they were not, in fact, making the decision to inflict pain; they were merely acting as agents of a superior decision-maker.

In studies by Bressler, B. et al (Katz, pp. 365-369) traumatic neurosis was deliberately induced by placing normal subjects in an environment of sensory deprivation. Some of the subjects manifested lingering disturbance after the experiments terminated. The investigators concluded, among other things: "Although the problems indicated were naturally latent, we believe they would not have emerged with the same intensity in ordinary circumstances."

Some experiments with hallucinogens and psychotomimetics have produced prolonged and, at times, serious behavioral aberrations. The risks and benefits of psychosurgery will be the subject of another paper.

There are also a variety of derivative psychological risks. For example, the successful treatment of an alcoholic or a neurotic may--in the view of his or her spouse--change that individual to someone whom the spouse "no longer knows". This, in turn, may precipitate divorce or various other personal dislocations.

Many investigators pre-screen prospective subjects to see if they are "fit" for participation in the research. Some of the effects of this pre-screening for psychological studies may be quite traumatic. For example, in one study prospective subjects were informed that the investigators wanted to show a stress-provoking movie to "normal" individuals to determine their

physiological reactions to the stress. They were further informed that prior to viewing the movie they would have some standard psychological screening tests. After these tests some were informed that the investigators had decided--based on the results of the tests--not to proceed to show them the movie. One can imagine the reaction of these prospective subjects who--by implication--were informed that they had been found psychologically unfit to see a movie.

The phenomenon of rejection based upon "failure to pass" pre-screening tests for "normality" is not limited to psychological research. Many persons who assume they are healthy learn through such tests that they have various chronic diseases. Is this a harm or a benefit?

Many types of biomedical research interventions that are not directed at the subject with a known behavioral disorder have proved, over the years, to present serious psychological risks, some of which were reversible and some of which were not. Thus, it was not anticipated that the administration of reserpine for purposes of treating hypertension would result in a significant number of individuals in a rather precipitous development of severe--and often agitated--depression; some of these individuals proceeded to commit suicide before the physician-investigator was even made aware that depression existed. Similarly, during the early developmental stages of palliative surgery for Parkinson's Disease and cerebral angiography some individuals were left with serious, and often irreversible, behavioral deficits.

Serious psychological problems are occasionally presented to certain susceptible individuals just by virtue of being made aware that they are research subjects. Some people find it quite stressful to know that they

are venturing into the unknown; this is particularly true in situations in which in order to become research subjects they must agree not to avail themselves of "established" diagnostic or therapeutic alternatives. The stress they experience may be manifested as any of a variety of behavioral aberrations or psychosomatic complaints.

One psychological reaction that arises fairly commonly in relation to agreement to participate as a research subject is guilt ^(self-blame). When an individual consents to research upon his own person there may be some motivating factors in his agreement to become a subject which may or may not be discussed frankly during the consent negotiations. Thus, at a time when "standard and accepted" therapy for a melanoma on the thigh was considered amputation of the entire hindquarter, an avid golfer who was invited to participate in a comparative trial of local excision might have a problem. He might be motivated to partake of this relatively untested therapeutic approach largely because he wanted to continue to play golf. On the other hand, he might wonder whether he was behaving responsibly in relation to his family and friends by agreeing to take what might prove to be a greater risk of dying of the disease. A somewhat analogous situation might be seen in a woman with breast cancer who agrees to participate in a clinical trial of "lumpectomy" at a time when--as she understands it--the standard and accepted practice is radical mastectomy. The primary and perhaps undisclosed motivation for her consent is cosmetic.

Even if there is relatively no guilt at the outset there may be severe guilt reactions if the risk actually becomes manifest as harm. Thus, if the individuals mentioned in the preceding paragraph subsequently are informed

that they have metastatic tumors they may develop the belief--which might or might not be appropriate--that if only they had chosen to proceed with the standard and accepted therapy they would not be in their present predicaments. It is an easy step from there for the subject to equate his decision with one to commit suicide. In these cases the guilt reaction becomes manifest only if the cancer recurs. The very same individuals might be quite pleased with themselves if five years later there was no evidence of recurrent tumor and they were much less incapacitated or deformed by the "experimental" surgery than they would have been by "standard and accepted" therapy.

This potential for guilt occurring as a consequence of an experimental failure is, of course, not easily predictable. To cite two studies the outcomes of which are now known: The parents who agreed to have cortisone (standard and accepted therapy for acute rheumatic fever at the time) withheld from the treatment of their children with acute rheumatic fever subsequently must have been very pleased to learn that the study proved that the hormone was ineffective for that indication; their children received the benefit of not sustaining all of the adverse consequences of cortisone administration. They must feel that they made a "good" decision. On the other hand, consider the study in which antibiotic treatment for streptococcal pharyngitis was deliberately withheld. The young men who developed glomerulonephritis (a serious and sometimes lethal kidney disease) probably felt that they made a "bad" decision. They are probably not particularly relieved to learn that they contributed to our understanding of which strains of the organism are most likely to produce glomerulonephritis.

The problems of guilt on the part of the consentor when risk becomes manifest as harm are probably even more serious in situations in which proxy consent was given.

In some situations the process of negotiating informed consent may be quite threatening. A physician-investigator may approach a patient with cancer for purposes of asking him to participate in a clinical trial. The investigator may assume incorrectly that the patient "knows" he has cancer because his personal physician has informed him. Thus during the process of informing for purposes of soliciting consent the patient may be deprived of the defense mechanism of denial.

In some situations--in the judgment of an IRB--the consent negotiation has been even more risky than the actual proposed research. An example of this was a proposal to approach individuals with suspected or proved acute myocardial infarctions shortly after their admissions to coronary care units with a proposal to do research that bore modest risk. It was the judgment of the IRB that the anxiety that might be produced in the patient by subjecting him to the necessity to make such a decision might be substantial. Conceivably--although this cannot be proved--the degree of anxiety that might be produced might contribute to the development of further damage to the heart or to the development of "coronary care unit psychosis".

Distrust is another reaction that can be precipitated in individuals by research. The decision to classify distrust as a psychological risk to the subject is arbitrary. This phenomenon has ramifications in the categories of

social risk to individuals as well as risks to society.

Let us first consider how distrust might develop in the individual as he is being asked to consent to become a research subject. The individual might perceive, often quite correctly, (cf boundaries paper) that the role he is being asked to play (subject) differs in some important way from the role he expected to play (patient). Thus, to some extent, the professional with whom he interacts might see the development of new knowledge as being an important goal which might compete with the goal of proceeding most efficiently to restore the health or well-being of the patient. Some subjects verbalize this as being used as guinea pigs.

In most consent discussions it should be made clear to the prospective subject that he has the right to refuse to become a subject. In fact, when the subject has a relationship with the investigator which has any potential for coercion there is usually added to the consent form a "non-coercive disclaimer". Such relationships might include physician-patient; employer-employee; faculty-student; and so on. When such relationships exist it is ordinarily stated on the consent form (or in the consent discussion) that the prospective subject is free to refuse to participate in the research and, further, that he is free to withdraw from the research at any time. Further, there is an assurance that such refusal or withdrawal will in no way adversely prejudice his future relations with the investigator or the institution. Thus, for example, if he is a patient, refusal to become a subject will not in any way adversely prejudice his status as a patient. One wonders how often a patient upon reading such language questions (perhaps not aloud) whether the physician-investigator is capable of experiencing rejection (refusal

to consent to become a subject) without retaliating in kind; ie, rejecting the patient in some way by becoming less responsive to his demands or wishes. Thus, a subject who has not been coerced might feel that he has or might have been. This, in turn, sows the seeds of a breakdown in trust in the relationship between the professional and the individual.

Similarly, the knowledge that research is being done in an institution--eg, a university hospital--may create in the community a sense of distrust. In many communities it is "general knowledge" that if you go to a university hospital you will be used as a "guinea pig". It is not at all uncommon that people who are asked to become research subjects in a university hospital express surprise. They say, for example, that they didn't know that they would be asked and offered the option to refuse. They just assumed that research would be done on them--perhaps without their knowledge. The risk of this sort of misunderstanding is that some individuals may elect not to go to a hospital when they feel sick and this decision may be detrimental to their health.

Social risks

Social risks are inextricably entangled with issues of confidentiality. Thus, through research an individual may become identified as a drug or alcohol abuser; as a participant in various deviant sexual practices; as having any of a variety of diseases which may be deemed unacceptable by his family, social or political group; as having a higher or lower income than his colleagues might have predicted; as a felon; and so on. If such information becomes known to the wrong individuals it might cost the subject his reputation, job, social standing, credit, citizenship, and so on. Ob-

viously, this issue extends into the categories of legal, economic, psychological, and (rarely, one hopes) physical risk.

A somewhat less obvious social risk also involving issues in confidentiality and privacy is presented by the mode of access used by some investigators to prospective subjects. The investigators may attempt to secure the names of prospective subjects through hospital records, school records, social service agencies, and so on. Thus, when the prospective subject is contacted directly by the investigator, he may wonder what other aspects of the presumed confidential relationship had been violated. Such practices tend to undermine the confidence of individuals in health delivery, social service, and educational systems.

Legal risks

Legal risks are presented to subjects of social, behavioral and biomedical research. A majority of the legal risks might be viewed as a subset of social risks. Thus, through violations of confidentiality the subject may become liable to a variety of civil or criminal actions. The legal risks to the subject of social and behavioral research will usually be obvious to all concerned. The legal risks of some biomedical research may be more subtle (see social risks).

In some states (eg, Ct.) there are statutes which grant testimonial privilege as well as confidentiality to the psychiatrist-patient relationship. Others (eg, Ill., N.C., La., Pa., N.Y.) grant sharply limited testimonial privilege to the physician-patient relationship. Although no state grants privilege to investigator-patient relationships, there are federal research shield statutes providing limited protection particularly for patients and subjects in drug and alcohol abuse programs. Thus, there is the potential problem of law enforcement agencies gaining access to lists of names of known felons through subpoena of the records of an investigator:

eg, a clinical chemistry laboratory, a methadone maintenance program, or a criminologist.

Since a comprehensive review of the law as it relates to research is about to be published there will be no further discussion here. This book, entitled The Risks of Social Research, edited by Paul Nejelski and Batya Miller of The Institute of Judicial Administration, New York City, includes not only the papers presented at The International Conference on Research in Conflict with Law and Ethics (March 1974) but also a comprehensive review of statutes, regulations, and court cases in the field. The Commission may wish to examine this book prior to its publication.

Economic risks

Subjects may be called upon to pay for procedures that are undertaken with research intent. This is a particular problem in complex activities (cf, boundaries paper) with mixed intent in which it is not clear either to the investigator or the subject which parts of the activities are practice and which are research. Subjects may be called upon to pay for hospital services which would not have been necessary had no research been done. Also, subjects may suffer loss of income when they take time off from jobs to participate in research; they may also have to pay baby-sitter fees, and so on.

A more serious economic risk is involved in the payment for damages to the subject that may occur as a consequence of research. Since, as will be discussed later, it is society in general that derives benefit from most research, it seems appropriate for the economic risks to be distributed equitably. This might be accomplished through development of adequate insurance for research subjects. When research is sponsored by the government it may

be assumed that the benefits are in the public interest; in these cases one might expect the government to subsidize the insurance premiums. Similarly, when the research is sponsored by industry (development of drugs or devices) one might consider asking the involved industry to subsidize insurance premiums. This issue is discussed further under the heading of economic risks to society.

Through participation in research a subject may lose his insurability. This is at least a two-fold problem. First, in the course of research various diagnostic tests may be performed that, in the ordinary practice of medicine, would not be considered indicated. These tests may reveal diseases or susceptibility to diseases which--in the view of insurance companies--would call for either higher insurance premiums or refusal to underwrite life, health, or disability insurance. A second part of this problem is that in many institutions, research findings which are germane to considerations of health, are entered directly into the subjects' (patients') medical records. When the subject subsequently applies for insurance and signs a form allowing the insurance company access to his medical record he generally has no idea as to the quantity or quality of information thus disclosed.

Other risks with economic implications are discussed in the categories of social and legal risks.

There are also a variety of derivative economic risks some of which are obvious and some of which may be subtle. For example, some research is done without the awareness of some third party who might subsequently be asked to share the economic burdens imposed by failure of the research to accomplish the hoped for benefit. Thus, for example, in studies of post-coital contraceptives an unaware third party (coital partner) might (post hoc) be called upon to share the burdens (economic and decision-making) in regard to abortion or carrying a potentially damaged fetus to term.

Risks to society

The physical risks to society are, in general, those specified as derivative physical risks to the individual. One might also consider the physical risks to society that occur as a consequence of research which does not directly involve human subjects. Thus, pure laboratory research may develop an alien and particularly virulent strain of virus. An appreciation of the magnitude of this potential problem may be gained by considering the introduction of measles into previously unexposed populations by 16th century explorers. Dramatic fictional descriptions are contained in Crichton's "Andromeda Strain" and Szilard's "My Trial as a War Criminal". Here we might also consider the public health hazards inherent in disposal of "nerve gas" and radiation wastes.

The potentialities of developing alien viruses and antibiotic resistant bacteria are no longer the exclusive domain of science fiction. It was this sort of potential around which there was much debate in 1969-1970 when James Shapiro et al described their isolation of the pure lac operon; in connection with this controversy Shapiro quit science to enter politics (Science 167: 964, 1970). Subsequently the controversy was renewed in connection with a recognition on the part of molecular biologists of the potential biohazards of recombinant DNA (Science 185: 303, 1974). In the latter case, recognizing the grave potential for development of oncogenic and other viruses, antibiotic resistant bacteria, toxin producing potential of ubiquitous and ordinarily innocuous bacteria, and so on, the molecular biologists called for a moratorium on many aspects of research in this field. Another highly significant potential in pursuing this line of research is that there is the possibility of either deliberately or inadvertently altering the human genome. This latter possibility

has enormous ramifications that might more appropriately be discussed under the category of risks to society.

Psychological risks to society are in general those discussed as derivative psychological risks to the individual research subject; others were presented as social risks to the individual--the consequences of the two types of violation of confidentiality.

Premature (or otherwise inappropriate) dissemination of either the findings or the opinions of researchers may present psychological risks. Thus, for example, phobias may be developed on a rather grand scale when the public is informed that low-cholesterol diets may cause cancer; that small breasts are associated with low I.Q.; that citizens of certain cities (e.g. Dallas) are susceptible to violence by virtue of low lithium content in the local water supply, and so on. On the other hand, false hopes may be raised by premature or otherwise inappropriate dissemination of either the findings or opinions of researchers. Consider, for example, how many different surgical "cures" for coronary artery disease have been discovered and abandoned in the past 20 years. Thus far we have discussed only the activities of "legitimate" researchers; one might also consider the consequences of public announcement of such "miracle-cures" as Krebiozin (for cancer), copper bracelets (for arthritis), rainbow pills (for obesity), and so on.

Social risks

It is often asserted that the major burdens of direct risks to subjects are borne disproportionately by certain socio-economic groups. The Commission's studies of IRBs should indicate whether these assertions are true.

Studies designed to compare certain social, ethnic, racial, religious, or political groups may develop findings which--in the view of some members of a

group--might have pejorative implications. Others in the same group may view the same results as beneficial to the group. For example, when research revealed that the incidence of suicide was much higher in female physicians than in male physicians some female physicians found this to be pejorative and supporting the "male-chauvinist" cause. Others welcomed the information as beneficial supporting their efforts to develop constructive affirmative action plans. Similarly, in a non-research context, some individuals perceive plans to offer abortion and sterilization services in publicly-funded health care delivery systems as attempted genocide. Others in the same groups perceive regulations to proscribe such activities as depriving them (as a class) of their rights to benefit from technology available to others to aid them in what they consider rational family-planning.

Another line of research that presents considerable risk to society as well as to certain individuals within society is that in which an attempt is made to predict certain characteristics of individuals or group of individuals by genetic screening. Thus, for example, there is the recent renewed interest and controversy over attempts to link XYY chromosome patterns with criminal behavior (Katz, pp 342-346). The unfortunate consequences of this research and the publicity it received has been reviewed recently (Science 188: 1284-1285, 1975). Another related piece of research which has received considerable publicity is the report that the same chromosomal markers can be used to predict race and IQ; what was demonstrated was that there seemed to be a correlation between one particular race and a low IQ (see for example Lubs et al: Amer. J. Human Genetics 25: 47 A, 1974).

Another type of social risk is that some research either by its very nature or by the sometimes callous manner in which it is performed may shock the sensibilities of society (or some subsets thereof). Historically, public sensibilities as they were perceived about 20 years ago, caused investigators who were then developing oral contraceptives to conduct the early clinical trials in Puerto Rico. One doubts that this would be necessary today. In its time the "Kinsey Report" offended the sensibilities of many citizens. At the time the "Masters and Johnson" work was being publicized almost no one would have considered the "Kinsey Report" offensive. Similarly, the second "Masters and Johnson" report shocked public sensibilities at a time when the first report would probably have shocked very few.

In some cases relatively little issue might be taken with the actual research but rather with the apparently callous manner in which it was performed. Thus, graphic descriptions of decapitation of dead abortuses have shocked public sensibilities; possibly the very same research--done with greater sensitivity--would have attracted little or no attention.

There are some sorts of risks to society that may be so large as to constitute absolute barriers to proceeding with research. Whether or not it is appropriate to incorporate these as risks for purposes of entering them into the calculation of risk-benefit criteria will be discussed later. One of the sorts of risks is presented by research that would change our perception of what constitutes a person.

The heated controversy that can develop as to what constitutes a person

was recently well illustrated for the Commission in the debates about fetal research. On one extreme there were ethicists and others who firmly asserted that a person begins to exist at the time of conception or, alternatively, at the time of implantation. On the other extreme there were those that supported the concept that all of the attributes that constitute personhood have not developed until approximately age 1½ to 2 years. A third point of view was that one might finesse the debate by classifying personhood as a "premature ultimate".

Depending upon ones definition of personhood together with the principle that a human person bears a value that takes precedence over all other values it was asserted that under no circumstances could one deprive a person of his life in order to achieve some goal (eg, a research objective). Similar debates were conducted in the recent past about developing definitions of death which would permit harvesting of viable organs or tissues for transplantation purposes. It seems unnecessary to recount these debates here.

Similar debates have begun and may be expected to intensify as the potentialities for genetic-modeling, cloning, hybridization with other species, and so on become closer and closer to being technically feasible.

Another sort of closely related risk to society[^] is presented by actions which may tend to erode the bonds of trust that one ordinarily assumes. This has been discussed in other sections in relation to eroding the bonds of trust between individuals and various institutions. In the research context one is particularly concerned with the authority to give proxy consent. Thus, as there is a growing public awareness about the possibility to give proxy

consent to risky research, there may be a gradual erosion of the bonds of trust between those with limited capacities to consent on one hand and, on the other, those authorized to--or even held responsible for--giving such proxy consent.

The issue of distrust was discussed to some extent under the rubric of psychological risks to subjects. It was pointed out that this issue also had ramifications in the category of social risks to society. Thus, for example, it was pointed out that in some communities it is "general knowledge" that if you go to a university hospital you will be used as a "guinea pig". In that situation--particularly when individuals are admitted to university hospitals--the phenomenon of distrust can be--to some extent--dispelled through the process of informed consent.

Now, let us consider the social risks in cases in which truly informed consent cannot be (or is not) secured prior to initiating the research. This sort of research is common in some social and behavioral sciences. For example, in some sorts of research--the so called "unseen observer" type of research--the experimental subjects are not even aware that research is going on. A good illustrative case is presented by Humphreys "Tearoom Trade" studies (Katz, pp 325 et seq). This sort of research presents several risks to society. In this particular case the "subjects" were practicing homosexual acts in public restrooms. Such acts were at the time classified as felonious in the city in which the research was done. The risks to the individuals of violation of confidentiality have been discussed elsewhere. When the results of the research became publicized it is quite likely that many homosexuals became distrustful of a society in which

they might be observed without their awareness. They must have been particularly frightened that they might be--as a consequence of such observation--convicted of felonies. This type of "unseen observer" research has been repeated in many environments and there is a growing awareness of the possibility that one might--at any time--be observed while engaging in activities one might have considered private.

Other such studies have involved recording of the deliberations of juries (Katz, p. 67 et seq), and so on.

The "Tearoom Trade" studies also afford an opportunity to discuss two additional types of risks to society which may occur as a consequence of conducting social research. During the course of these studies the investigator recorded the license plate numbers on the automobiles of the individuals whom he was observing. Through contact with the motor vehicle registration authorities he identified these people by name and address. He was then able to make personal contact with them and then--with their informed consent--conduct his in depth studies. However, it is conceivable that some individuals so identified might have objected and might have developed the same sorts of distrust mentioned earlier in relation to access problems when hospital, school, or welfare records are used.

A second phenomenon observed by Humphreys and several other investigators may be considered. When an investigator (or a type of investigation) becomes well known it may be assumed on the part of some that the institutions or groups of people he spends time with have a high incidence of the sorts of people known to be of interest to the investigator. Thus, if Humphreys is observed spending time at a certain institution it may be assumed by those who

observe him that that institution has within it a large number of homosexuals. This becomes a particular problem when law-enforcement agents become aware of the activities, interests, and whereabouts of certain investigators who wish to study criminal behavior. Thus, for example, an investigator who was known to be studying drug abuse patterns in a public high school would tend to focus police attention on that high school and increase their surveillance and questioning of students in that particular high school. Parenthetically, it might be noted here that some investigators have been threatened with criminal liability if they did not reveal the names of those they observed engaging in criminal activity.

In cases in which video-tapes are made of individuals engaged in what they believe to be private acts the same issues of distrust are raised. However, in these cases protection of privacy becomes more problematic. It is possible to remove an individual's name from a questionnaire. However, faces and voices are sufficiently distinctive so that it may become impossible to obscure the identity of those who were taped (video or audio). In such cases informed consent may be secured following the taping; the classic paradigm of which most members of the public are aware is "Candid Camera". A prevailing awareness that one might at any time be observed, recorded, or bugged, may have a detrimental effect on the behavior of many individuals. An extreme example of the potential impact of such activities on a society is described by Orwell in "1984".

Some anthropologists by joining a society may actually change the nature of the society. There may be considerable debate as to whether the changes are detrimental or beneficial. An awareness of this potential is expressed in

the actions of the Phillipine Government to limit access to the Tasaday Group.

Some additional discussion of the general risks and benefits to society of social research was presented earlier in the "boundaries paper".

Legal risks

In the criminal justice system, society customarily views convicted criminals as its adversaries. Thus, to the extent we develop research shield privileges we may be imposing a risk on society. Also, one might consider here the civil legal risks to the institutions that are performing the research. For example, if an investigator is sued for malpractice (or malresearch) while operating according to a protocol approved by an IRB, to what extent do members of the IRB share the burden of this legal risk?

Economic risks

The actual cost of doing the research might be considered society's "risk-capital" to develop information based on the assumption that the information will benefit society. Thus one criterion for determining the appropriateness of the proposed activity might be: Is the information we might develop worth that much money? For an interesting and provocative analysis of how society responds to such questions see Calabresi, G. (Katz pp 177-184).

Another type of economic risk borne by society is the cost of "taking care of" individuals who are damaged by research. Here one is particularly concerned with physical and psychological damage to research subjects. At the very least, someone has to pay for the medical or psychiatric care ne-

cessary to treat the conditions induced by experimental interventions. An even more serious (though presumably rare) threat is that of dealing with an individual who as a consequence of research becomes permanently disabled. Thus, through research, it is conceivable that one might take previously normal and productive individuals and--by virtue of having induced paraplegia, psychosis, drug-addiction, and so on--add them to the ranks of those who must subsist on welfare.

The problem of insurance for research subjects is currently being studied by the Secretary's (DHEW) Task Force on the Compensation of Injured Research Subjects. This task force is headed by Seymour Perry, M.D., Special Assistant to the Director, NIH, in the Office of Program Planning and Evaluation, Office of the Director, NIH. The orientation of this task force is to develop a system of insurance that would compensate research subjects for harm that befall them as a consequence of research. They are oriented toward developing the insurance on a "no-fault" or Workmen's Compensation Model. At the time of this writing they do not seem near the point at which they might make final recommendations. Apparently, they have encountered some difficulty securing reliable data on morbidity and mortality rates for research subjects. Perhaps the Commission would wish to establish formal communications with this group.

Another approach to coverage has been developed at several institutions. Thus, for example, the University of Washington (Seattle) has research insurance underwritten by a private company (Aetna). As I understand it this insurance is based on a no-fault model and is developed along the lines of the state Em-

ployee's Compensation Act. One difficulty with this approach is that it covers only individuals who are classified by state law as employable; ie, children would not be covered.

Some other universities have their general malpractice coverage extended to cover the activities of physicians who are engaged in research. In general, this is a fault model. A claim must be made against the physician-investigator and/or the institution; the settlement of the claim is, in general, determined as in most malpractice claims.

Risks of not doing research might also be considered at this point. The risks essentially will be a deprivation of society of the benefits to be described subsequently. Here one is faced with the difficulty of anticipating the outcome of future research. Thus the approach probably should be to analyze what the risks might have been if some sorts of past research had not been done. Examples that might be used include the development of various sorts of immunization procedures (vaccinia, rabies, and polio provide dramatic examples), general anesthesia, antibiotics, laparotomy, heart surgery, amniocentesis, and so on. The "therapeutic-orphan" phenomenon has been discussed in relation to research on the fetus and undoubtedly will be raised again in considerations of research on children; it is a harm of not doing research.

BENEFITS

At the outset it should be made clear that there is no way to separate the issue of quality of scientific design of research from the ethical considerations as to whether it should be done. If research is badly designed it is not likely to benefit anyone. Thus, it seems inappropriate to put human beings at risk to develop information (or misinformation) that cannot conceivably benefit either the individual or society. This principle is clearly

enunciated in the Nuremberg Code. The principle is extended in that Code as follows: "The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment." Principle 7 of the same Code requires that: "Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death." Subsequent commentators have extended this latter principle to mean that the facilities available to conduct the research should also be adequate to assure successful completion of the experiments. Thus, an important criterion of whether it is appropriate to proceed with a particular research proposal is that the experiment has been well-designed; the investigators who plan to execute it have appropriate skill; and the facilities in which the experiments are to be conducted are optimal not only to achieve the scientific objectives but also to protect the rights and welfare of the subject.

Principle 3 of the Nuremberg Code reflects the context in which it was written and clearly is not applicable to all research to be considered by the Commission. "The experiment should be...based on the results of animal experimentation...". This principle, in cases in which it is applicable, is in part an issue in scientific design. The purpose of preclinical animal testing is to develop information that permits better design of experiments to be done on humans. Among other things, preclinical testing in suitable animal models enhances ones power to predict the outcome of performing the same intervention in a human. In some cases, the results of studies intended

to be preclinical will indicate that the experimental modality should not be tested in humans.

One issue that may be separated from that of scientific design might be stated as a corollary to parts of Principles 2 and 3 of the Nuremberg Code: It is inappropriate to put humans at risk to gain information that can be secured without putting humans at risk. This issue will be discussed further in a subsequent paper.

Benefits to society

The discussion of benefits will be even more superficial and general than that of risks. This reflects the bias of the author that those who review research proposals to determine their "appropriateness" will almost always find the benefits or hopedfor benefits clearly described. There is further a tendency to overestimate the probability of achieving the hoped for benefit. By implication it is suggested that risks tend to be underestimated. This does not reflect dishonesty; rather it reflects the facts--in the opinion of the author--that most investigators are focusing on the benefits and many are either unaware of or inattentive to some of the phenomena described as subtle risks.

The benefits to society will be discussed for 4 broad categories of research: 1) Applied biomedical and behavioral research (performed with the intent of developing or perfecting diagnostic, prophylactic and therapeutic modalities) (this category is similar to innovative therapy (boundaries paper)); 2) Basic research involving human subjects (done with the intent of improving our understanding of the biology and psychology of normal and "abnormal" human beings); 3) Basic research (not directly involving human subjects); and 4)

social research.

1) In general, the benefits of applied research involving human subjects will be obvious. It is in the interest of society to develop improved techniques and technologies for the diagnosis and treatment of disease. However, one must be cautious to acknowledge the fact that it will be easier to demonstrate the benefit to society of research in general than of any particular proposed research project. Thus, historically, one can review research in a field (eg, development of antibiotics) and show the enormous benefits that have accrued to society through the development of penicillin, tetracyclines, and so on. However, some equally well-conceived research projects have yielded no valuable drug. All research is conducted with an awareness of the a priori assumption that one does not know in advance what the outcome will be of that particular experiment. Thus, when speaking of a particular research proposal one can only discuss potential or hoped for benefit.

Well-done research that proves with certainty that a specific diagnostic or therapeutic maneuver is not valuable (not safe or not effective) also benefits society. The benefit, in fact, may be even greater than that deriving from "successful" developmental research. It may save society the cost of further development of the unsafe or ineffective modality. It may further save individuals the risk of being exposed to the intervention found to be either unsafe or ineffective.

Benefits of research in this category have major economic and social implications. Economically, one might consider the amount of money saved by virtue of development of successful immunizations to polio or rubella.

From a social point of view one might consider how the development of improved technology changed the social status of individuals who contracted leprosy or syphilis. One might also consider how the development of psychiatric techniques first changed the social status of individuals once branded "insane" and subsequently, the economic and social implications of the development of phenothiazines.

2) Basic research involving human subjects designed to develop improved understandings of the biology and psychology of normal and abnormal (diseased) human beings. Ordinarily, this research offers no direct^{health} benefit to society or to the individual. However, without this research, ^{little} research in category 1 is possible. Thus, the derivative benefits are those of category 1; however, it is a useful exercise to remind ourselves that the potential benefits of research in category 2 are more remote than are those described for category 1.

3) Basic research not directly involving human subjects. When one considers this sort of research in the context of providing a fundamental basis of knowledge on which research in categories 1 and 2 might be derived, one usually considers studies done on "animal models" of human diseases; basic pharmacological studies, basic virology, basic psychology, and so on. Other studies that are obviously connected include some which do not even involve intact animals; eg, basic enzymology, studies of cerebral synaptosomes, and so on. However, it may be appropriate to consider almost all research as potentially providing health related benefits to society as insights are developed to form the basis for research in categories 1 and 2. Thus, for example, one might trace the tortuous history of research designed

to develop rocket fuels resulting in the development of drugs (monoamine oxidase inhibitors) which are now used widely in the treatment of depression. Similarly, "mustard gas" was developed as a weapon for World War I; studies on its effects by various types of investigators resulted in the development of our first effective cancer chemotherapeutic agent. The development of cortisone and related hormones was expedited enormously on the basis of (admittedly erroneous) reports of spys that the Germans (then our enemies) had demonstrated that adrenal cortical extracts enhanced greatly the stress tolerance and stamina of Luftwaffe pilots. Anthropologists have made multiple contributions; eg, the description of the use of the Calabar Bean as an "ordeal poison" in trials for witch craft in some remote tribes in West Africa. This, in turn, led to the development of physostigmine--our first effective anti-cholinesterase. Subsequent research in the same area also led to the development of the organophosphates, one of which, DFP, not only is effective in the treatment of glaucoma but also is the widely publicized "nerve-gas".

4) It might be appropriate to sub-divide social research as we have biomedical and behavioral research. Thus, applied social research might be discussed as was applied biomedical and behavioral research (performed with the intent of developing or perfecting diagnostic and therapeutic modalities). An attempt to develop this analogy was presented in the boundaries paper. Thus, a social scientist may somehow perceive that there might be some societal dysfunction. His research may be designed to describe or analyze this dysfunction sufficiently adequately so that he might recommend a "remedy". This remedy might be actualized by changing public policy or by changing the procedures within an institution.

The second category of social research might be analagous to category 2 of biomedical and behavioral research. That is basic research involving human subjects (done with the intent of improving our understanding of the structure and function of various societies, institutions, and so on). This sort of research often forms the basis or provides the research "leads" for the activities of applied social researchers.

Another benefit to society of social research is that it enriches our understanding and enjoyment of our selves, our species and our interactions. It is difficult to assess this either quantitatively or from a utilitarian point of view. But how many people who will never go to Samoa have enjoyed M. Mead's books? How many are fascinated by The National Geographic? On the other hand, when E. Bowen (L. Bohannon) wrote Return to Laughter she could not have imagined that it would one day be used in the orientation of Peace Corps volunteers going to Nigeria.

As the Commission has observed earlier: "Scientific inquiry is a distinctly human endeavor." (Research on the Fetus, p 63). Through publications of the sort mentioned above, nonscientists may participate vicariously in these distinctly human endeavors.

Obviously this benefit is not limited to social research.

Benefits to subjects

Direct health benefits

It will be more difficult to describe benefits to subjects than to describe benefits to society. As mentioned earlier, all research must proceed with the a priori assumption that one does not know in advance the outcome. This becomes a particular problem in discussing with individual subjects the potential benefits of simple (as defined in the boundaries paper) activities. This is not

to say that one does know with certainty what the outcome will be--what the direct therapeutic or diagnostic benefit will be--of a simple activity that has been classified as standard or accepted. However, by the time a simple activity has been classified standard or accepted it is ordinarily possible to inform the patient what the probabilities are of direct therapeutic or diagnostic benefit and what the probabilities are of adverse effect. It also is at this point possible to present a reasonably comprehensive list of what the beneficial or adverse effects might be.

Before discussing this issue further it might be of value to re-examine the concept of innovative therapy described in the boundaries paper. The ability to predict diagnostic or therapeutic benefit proceeds along a continuum. During the earliest stages of working with a innovative diagnostic or therapeutic technique, ones ability to predict the outcome is very small--in many cases it approximates zero. With successive repetitions of the innovative intervention the power to predict the outcome increases. By the time a procedure ceases to be considered innovative--the point at which it is considered standard and accepted--the power to predict the outcome of its implementation is ordinarily nearly as high as it will ever be; it is virtually never 100 per cent. Clear exceptions to the preceding statement exist. Thus, for example, after a modality is considered standard or accepted, continuing investigation or experience may change our understanding of what the outcome of its implementation might be. Thus, new toxicities or new benefits might be discovered.

One may acknowledge the fact that in consideration of complex activities

(cf boundaries paper) it may be appropriate to tell the prospective subject that there will be direct diagnostic or therapeutic benefit. However, the benefit will ordinarily derive from those aspects of the complex activity that may be considered practice rather than research. For example, if one wishes to study the effects of chlorothiazide (a diuretic) on sodium balance in patients with congestive heart failure and if one selects subjects in whom chlorothiazide is indicated and administers the drug in appropriate doses, the subject may receive direct therapeutic benefit. This study might be accomplished in a metabolic research ward. It might involve a period of two or three weeks of eating a constant diet with precise control of sodium content. It might involve repeated samplings of venous blood and collection of all urine excreted during those two or three weeks for purposes of sodium assay. The patient may be expected to receive direct therapeutic benefit through administration of the drug; however, this is only technically a research intervention. The subject will not benefit ordinarily from repeated blood sampling and urine collection. The subject may or may not benefit from the constant diet; it might be more or less nutritious and/or palatable than the diet to which he is ordinarily accustomed. The subject might also benefit from a two or three week period of relative rest on a metabolic research ward. If the subject required hospitalization for that long a period of time anyhow it is likely that he will find the accommodations better on the metabolic research ward than on the usual hospital ward; however, this is not true in all hospitals. If the subject did not require hospitalization for therapeutic purposes, the period of incarceration might be viewed more as an inconvenience than as a benefit. Further, owing to the customary practices of very careful scrutiny of all activities on metabolic research wards, the subject might derive

additional benefits as follows: Any adverse effects of the chlorothiazide are likely to be discovered earlier than they would in the course of the ordinary practice of medicine. Thus, the risks of taking the drug would be reduced accordingly. Further, any complications of the subject's basic disease are likely to be found and tended to quite promptly. Additional ramifications may be provided if desired. Also, additional examples may be provided. However, this illustration provides a general paradigm of the sorts of direct health benefits that may accrue to a subject of research.

Cohen:
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The Hawthorne effect (Levine, and Clinical Research 22: 111-112, 1974) which is well known to social scientists also greatly influences the outcome of many behavioral and biomedical research activities. Thus, it is often found that patients in a research environment seem to do better than patients receiving the same intervention in a practice environment. The probable explanation of this phenomenon is that subjects respond to the enthusiasm and optimism of the personnel found in the research environment. A dramatic example of this may be found in the studies of Rashkis and Smarr (Arch. Neurol. Pschiat. 78: 89-94, 1957).

To this point we have been concerned with the direct benefits that may accrue to a subject by virtue of his participation in either biomedical or behavioral research. The benefits may be analyzed similarly whether the research is in the biomedical or in the behavioral field. Subsequent discussion in this paper will be concerned with benefits categorized as follows: Psychosocial, economic, and derivative. It should be made clear at the outset that

discussion of these benefits is not meant to be a discussion of the benefits of either psychosocial or economic research; rather, it is meant to be a discussion of benefits of any biomedical or behavioral (and, to a limited extent, social) research; ie, what is being discussed is the category of benefit and not the category of research. It should further be understood that as one moves along the spectrum from direct health benefits to the other categories of benefits in the order listed there will be an increasing tendency to view these benefits as coercions. Specifically, explicit or implicit offering of these benefits during the process of negotiating with a prospective subject to obtain informed consent may be coercive. This paper will not deal further with the extent to which they ought to be considered coercive or whether use of such coercions is appropriate.

Psychosocial benefits

Some direct psychological benefits were discussed earlier in consideration of direct health-related benefits. These might be illustrated more dramatically if instead of considering the use of chlorothiazide in a complex activity we used for purposes of illustration of chlorpromazine, shock therapy, or T-groups. Similarly, the general improvement in morale implicit in the discussion of the Hawthorne effect may, to some extent be considered a direct psychological benefit.

The foregoing is essentially a shopping-list of other sorts of psychosocial benefits any or all of which the Commission might wish to explore in detail. Patients who know they have terminal illnesses and patients who are depressed for any reason will often respond favorably to the notion that investigators are not only interested in them but also attempting to devise something that

might offer relief or, perhaps, cure. Some patients with cancer in whom all "accepted" modes of therapy have been tried without success will experience a psychological "lift" when the option of trying an experimental drug is offered. In this context the patient (now become subject) may be relieved to learn that he need not give up hope as there is yet another possibility for relief (cure?). Further, the subject will often be relieved to learn that he is not about to be abandoned by the physician (now become investigator). Many individuals who are either depressed or anxious (or both) will experience relief as they assume the role of subject; in the relatively sheltered research environment they are largely divested of the burdens of some sorts of decision-making.

Individuals who are concerned about their sense of worth may welcome the opportunity to appear valuable to themselves as well as to others. Often they may achieve an enhanced sense of personal worth through doing something that they consider altruistic. Among the obvious examples of such individuals are prisoners (who might, incidentally, hope that their altruistic tendencies will be appreciated by those who make parole decisions) and some women who are about to have abortions.

In some social groups playing the role of subject may bring an individual considerable prestige. Here we are not only talking of sociologists who might consent to playing the role of biomedical research subject in order to complete doctoral dissertations. There are ordinary citizens who are flattered to be the subject (or object) of attention of so many "important" people. This is particularly true of individuals who become eligible for the role by virtue of having a rare disease. Other persons gain what they consider to be

substantial prestige or satisfy their tendencies to exhibitionism through participation in research that attracts great publicity; eg, Reed's studies on yellow fever, open-heart surgery, kidney transplants (particularly the role of donor), and so on.

Economic benefits.

The most obvious economic benefits are direct cash payments to the subjects. Some individuals who are filling the roles of both subject and patient in complex activities may be offered free health care most or all of which they would have had to pay for themselves had they not agreed to play the role of subject. Consent to play the role of subject may afford the individual access to improved accommodations in hospitals, prisons, or other institutions; to better food and/or medical care or to improved prerogatives of various sorts when the investigator and subject simultaneously play any of the following combinations of role-relationships: doctor-patient, employer-employee, teacher-student, warden-prisoner, and so on.

Derivative benefits

Let us now consider the benefits of research which brings no personal health or economic benefit directly to the individual who volunteers to play the role of subject. Here we will be concerned with what the subject experiences as personal benefit as a function of his sense of kinship with the individuals who might derive direct benefits. To some extent derivative benefits intersect with some phenomena described as psychosocial benefits. To the extent that the subject feels a sense of kinship with larger and larger groups of humans (the largest group being the entire human species) the motivation increasingly approximates pure altruism. As discussed earlier, a sense

of altruism may in some cases be experienced as a psychosocial benefit.

Perhaps the closest sense of kinship one might feel is with ones self. Thus an individual might be motivated to take risks as a subject of a study (category 2) designed to explore the biology of the disease with which he is afflicted. The hoped for benefit might be that--based upon the basic knowledge developed in the course of this research--subsequent research might develop a therapeutic intervention that would provide a direct health benefit to him. Alternatively, the subject might feel a sense of kinship with others with the same disease hoping that in the future some direct benefit might accrue to them. Derivative benefits in this category are most likely to influence individuals with prolonged chronic diseases. Thus, for example, an individual with cirrhosis may be motivated to take substantial risk--perhaps including serial liver biopsies--with the hope that information might be developed that would lead to the further development of a therapeutic intervention that might bring direct benefit to him within the subsequent 2 or 3 years.

Another close kinship relationship would be that of the family. This is particularly likely to be a motivating factor in consideration of research in genetics and transplantation. Thus an individual might be more willing to offer a kidney to a close relative than to a stranger. The father or mother of a child with phenylketonuria might be willing to participate in research designed to perfect techniques for detecting carriers even though it will bring no direct benefit to them or to their child; they already know they are carriers. However, if a better method for carrier-de-

tection might be discovered it might provide direct health benefit to another relative who is phenotypically normal but who might be a carrier.

Senses of kinship might be based on racial or ethnic factors. Thus, some Jews might be motivated to serve as normal controls for research designed to explore the pathogenesis or therapy of Tay-Sachs disease; blacks might volunteer for similar roles in research related to sickle-cell anemia.

Women who are about to have abortions may feel a sense of kinship with other pregnant women who expect not to terminate their pregnancies but rather to continue to term; among such women in the future might be the woman who is now planning an abortion. Thus, she might be motivated to participate in research made possible by virtue of the fact that she has planned to have an abortion and designed to develop knowledge that might be of benefit to pregnant women who expect to carry their pregnancies to term.

The preceding discussion of derivative benefit based upon "senses of kinship" is related to the arguments raised by Commissioner Lebacqz in which she invokes the "principle of proximity" (Research on the Fetus; p-87).

THE "ROLE" OF ASSESSMENT OF RISK-BENEFIT CRITERIA IN THE DETERMINATION OF THE APPROPRIATENESS OF RESEARCH INVOLVING HUMAN SUBJECTS.

The preceding pages represent an attempt to incorporate all of the factors that might be considered in determining the appropriateness of research involving human subjects as either risks (or in some cases costs) or benefits. Thus, it is now proposed that, when each of these factors has been considered adequately and assuming that one will not proceed without adequate informed consent, no other factors need be considered.

Ordinarily one would object to such a proposal on grounds that risk-benefit analyses used for these purposes have a tendency to become purely teleologic endeavors. Yet, there are incorporated under risks to society some of the sorts of issues that are commonly used in deontologic analyses. In particular, some sorts of activities that might erode our concepts of personhood or our assumptions of trusting relationships with one another and with various institutions ought to be given very heavy weight in the determination of the appropriateness of any particular research proposal. It may well be that one might wish to draw an absolute line as to how far one might permit these concepts and assumptions to be modified for research purposes. As was illustrated in the debates leading to the recommendations on the fetus it will be most difficult to achieve consensus on where the line ought to be.

Some other factors have been incorporated in the preceding discussion that are not necessarily considered by all as risks or benefits. To reiterate briefly: It was pointed out that research that is badly designed is not likely to yield any benefit either to the subject or to society. Thus, it was proposed that putting human subjects at risk in badly designed research is not ethical. This concept was extended as a requirement that research ^{that} puts human subjects at risk should not only be well-designed but also conducted by investigators who have sufficient skill and adequate facilities not only to conduct the research but also to protect the rights and welfare of the subjects. Similarly, it is inappropriate to put humans at risk to gain information that could be secured without putting humans at risk. Finally, reference was made to possible mechanisms for compensating individuals who might be harmed by re-

search.

There remain two additional problems: 1) Should one attempt to quantify the risks and benefits of any particular research proposal? If so, how? 2) Who has the authority or the responsibility to analyze the ratio between risk and benefit of any particular research proposal to determine whether or not it is appropriate to involve human subjects in it?

Definitions of role and appropriateness

The definitions of the words role and appropriateness are those contained in Webster's Third New International Dictionary. Since not all of the definitions contained in that dictionary are germane to the present discussion, the following is a clarification of which definitions are to be used.

Role, noun: 1a(1): A character assigned to or assumed by someone; (2): A socially prescribed pattern of behavior corresponding to an individual's status in a particular society. b(1): A part played by an actor; (2): A part assumed by a singer.

2: A function performed by someone or something in a particular situation, process, or operation (eg, the role of the teacher in the educational process) (the role of automobiles in leisure has been significant).

Definitions (1) and (2) under 1a will be important in discussing the roles played by various individuals and groups of individuals in making decisions on whether a particular research proposal is appropriate. Thus, for example, the IRB might be assigned the role of determining whether it is appropriate to invite an individual to become a subject of a particular research project. Similarly, that individual might be assigned the role of determining whether his participation in that particular project is appropriate (from his own perspective). In this process, each according to their (his) own criteria, the IRB and the prospective subject will have assumed or will have been assigned the role of decision-maker.

Definition b will be used to discuss the roles played by individuals in the process of conducting research; it will also be used to illustrate that

these individuals should be aware that alternate roles are ordinarily available to them. Thus, for example, an individual may choose to play the role of subject; alternatively, in some situations he might rather choose to play the role of patient. Similarly, the professional might have available to him the alternatives of playing physician or investigator or some combination thereof.

Definition 2 most closely approximates the meaning of the word when used to discuss the role of assessment of risk-benefit criteria...and so on. Here one is concerned with the function performed by something (in this case, assessment of risk-benefit criteria) in a particular process or operation (in this case, the determination of the appropriateness of research involving human subjects).

Appropriateness, noun: The quality or state of being appropriate.

Appropriate, adjective: 1: Specially suitable: Fit, proper. 2: Belonging peculiarly: Special.

In this paper, the word appropriateness will be used as a noun meaning: The quality or state of being fit or proper.

Parenthetically, it might be noted that the word, appropriate, is also defined in the dictionary as a transitive verb. The etymology of this word is very similar to that of the adjective. This word will not be used as a verb in this paper. It should be noted that the verb appropriate has for its synonyms: Preempt, usurp, arrogate, confiscate, pilfer and purloin. All of these verbs mean to seize or to take over more or less dictatorially. It should be clearly understood that none of these meanings are intended in the use of the noun, appropriateness, or the adjective, appropriate, in this paper. The connotations of the verb are in general the very things one wishes to avoid as one determines the appropriateness of research involving human subjects.

Quantification of risks and benefits

Current DHEW regulations (CFR 45 A, Section 46.2 (b) (1)) state the criteria for determining the appropriateness of research. In particular, it charges the IRB to: "(b) determine whether...subjects will be placed at risk, and, if risk is involved, whether: (1) the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks..." (Emphasis added). Additionally, HEW guides for preparing applications for grants or contracts (NIH Guide, Vol. 3, No. 12, August 26, 1974) require that the applicant: "6: Analyze the risk-benefit ratio." Implicit in these regulations and guidelines is the assumption that the IRB can balance in some formal or quantitative way the risks to the subject against the benefits not only to the subject but also--in the clause calling for importance of the knowledge--to society. The "guidelines" are not explicit as to how risk-benefit analyses are to be conducted.

One might infer from these regulations and guides that there is necessity for quantitative analyses of risks and benefits. Supposedly, if the benefits "outweigh" the risks one should make a decision to proceed with the research. Proposals have been made to analyze risk (cost)-benefit ratios according to some sort of formal mathematical equation. In general, what has been suggested, is that the decision-maker--whether it be an individual or a group--develop some criteria for assigning to any given predicted outcome a value; this value should be stated in numerical terms. Thus, risks would be assigned negative values and benefits, positive values. To derive a "sum" one would add together all of the values. Since, as has been discussed earlier, risk represents a chance of harm and most benefits--particularly benefits contingent upon the "success" of the experiment--must also be expressed as chance or probability of deriving benefit, each of the numerical values must be multiplied by some number (something between

zero and one) which expresses the probability of the risk becoming manifest as harm or the realization of various uncertain benefits. The various devices that may be used to attempt to express these analyses in quantitative terms are covered comprehensively by Wagner, H.M.: Principles of Operations Research, Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1969.

The fact that risks may be given different weights depending upon their probability on one hand and, on the other, their severity has previously been clearly expressed by the Commission (Research on the Fetus, Report and Recommendations, pp 83-85). This statement reflects the complexity of analyzing risks to the individual research subject--in this case, the fetus. It also reflects the fact that--even in this limited context--there is no way to assign either a weight or a probability to the risk of one particular harm; viz, the experience of pain. Of itself, this statement provides suitable cause for not attempting to determine risk-benefit ratios quantitatively. The difficulties in developing mathematical models designed to permit decision-making on a quantitative basis become increasingly complex as we attempt similar analyses of benefits (or probabilities of hoped for benefits). Attempts to balance risks to the individual against benefits to society obviously present even more of a problem.

At this point it seems appropriate to avoid using mathematical models to calculate risk-benefit ratios for purposes of determining the appropriateness of research. This statement should not be construed as opposing experimentation with such mathematical models. Continued attempts to devise such models may not necessarily result in the development of a suitable (safe and effective) decision-making model. However, attempts to devise such models often reveal to those participating in the attempt the information they lack--and, perhaps, should seek--which would permit "rational" decision-making.

What constitutes an adequate description of risks and benefits?

An adequate description of the risks and benefits of any particular research proposal should reflect a consideration of each category listed under risks and benefits not only to the subject but also to society. Ordinarily, this description will be provided in a protocol prepared by an investigator for review by an IRB. This assumes that all investigators proposing research on human subjects will be aware of all categories of risks and benefits germane to their particular proposals. This assumption is clearly not correct.

In general, the IRB (as a group) should be aware of each of these categories. Thus, as they review any particular research proposal, they should detect any categories that have been omitted and request of the investigator an adequate description of the risks (or benefits) in the omitted category. Such interactions between the IRB and investigators have the effect of educating all concerned (IRB members as well as investigators).

What constitutes an adequate description of any particular risk or benefit? In the preceding section it was suggested that each risk and each benefit might be expressed as a function of its magnitude multiplied by its probability. This suggestion--which sufficed for purposes of the preceding section--is an oversimplification. A truly adequate description of a risk or a benefit requires further analysis of both probability and magnitude.

An adequate description of the magnitude of either a harm or a benefit should include as complete a statement as possible of its expected duration. Thus, for example, if a possible harm is paralysis of one leg, how long is this paralysis expected to last? Certainly, the magnitude of the harm will be considered greater if the paralysis is ordinarily expected to last one year than if it were expected to last one hour. If the harm is ordinarily expected to

be irreversible--ie, expected to continue unabated for the duration of the subject's life--this represents the greatest possible magnitude of that particular class of harm.

In some situations, potentially irreversible harms, if detected early, may be either avoided entirely or reduced in magnitude. This avoidance or reduction may be accomplished by discontinuation of the potentially harmful research procedure. Alternatively, minimization of a developing or nascent harm may be accomplished by therapeutic intervention; eg, timely administration of an antidote to a "poison". In such circumstances a fully adequate description would include a listing of procedures that might be employed for timely detection of the developing harm. There should also be a clear statement of what criteria will be used to determine when to terminate the research or administer the antidote. There should further be an assessment of the probability and magnitude of success that can be reasonably expected of the monitoring procedures and corrective interventions.

Similarly, the magnitude of a hoped for benefit should be analyzed in terms of its expected duration. For example, if the research modality provides the hoped for benefit, what provisions have been made to assure the subject's continuing access to this (now proved beneficial) modality? The beneficial modality might be a drug or a device which proves effective (beneficial) in a particular subject but whose sponsor (eg, industry) decides to discontinue producing it because it has not been found beneficial to a sufficient number of individuals to make its further development worth the sponsor's investment. Alternatively, it might be an "experimental" health delivery system developed under public

funding in a community lacking the economic resources for its continuation at the termination of the period of public funding. For another example, the compensation for harm caused by research (payment for medical expenses, rehabilitation, and so on) may terminate (because the period of funding of the research has expired) before the rehabilitation of a particular harmed subject has been completed.

Similarly, the probability of the occurrence of both harms and benefits should ordinarily be elaborated. In consideration of harm, is there any means by which individuals who are most susceptible to harm might be identified? If so, will these means be used and will those individuals either be excluded from the research or informed that they are especially vulnerable? For example, in planning research designed to test the effects of strenuous exercise in "normal" humans, one would ordinarily plan to perform various screening tests to identify individuals with coronary artery disease in order to exclude them.

An even greater problem is presented when it is proposed to recruit research subjects from populations that either have limited capacities to consent, have subordinate relationships to the investigator or his institution (patients, students, employees, and so on), or--by virtue of other aspects of their life situations--are especially vulnerable (infra). The variety of problems mentioned in the preceding sentence are all to be discussed in detail in subsequent papers planned by the Commission. At this point, it should be noted that one of the factors that must be taken into account in determinations of the appropriateness of any proposed research is whether it is proposed to use as subjects individuals in these categories.

Existing and proposed DHEW regulations have identified as classes of persons having "limited capacities to consent" children, fetuses, prisoners, and the institutionalized mentally infirm. To this list at least the following should be added: the unconscious and the inebriated (by alcohol, marijuana, narcotics,

LSD, and so on). Other persons might be categorized as being especially vulnerable as a consequence of their life situations. For example, there are those who are legally enfranchised to give consent but in reality are incapable of sufficient comprehension to do so (eg, the adult mentally retarded and psychotics who have not been declared legally incompetent). Poor persons might be especially motivated to take risks in return for economic benefits. Persons having prolonged chronic illnesses (or other incapacities) may be highly motivated to participate as subjects of research that offers any possibility of relief. Further, they may be highly motivated to participate in research designed to develop basic knowledge which might subsequently be used to plan research designed to develop therapy for their conditions. This becomes a particular problem when such people perceive themselves as "desperate" and willing to take "any risk" for even a remote possibility of relief. In this category are some infertile persons or couples who "desperately" want a child; some persons with chronic, painful, and disabling disorders such as rheumatoid arthritis; some obese persons who cannot lose weight following standard procedures; and so on. Depressed persons and others who question their self-worth are peculiarly vulnerable (cf, psychosocial benefits). An especially vulnerable group are some of those who believe (correctly or incorrectly) that their own death is imminent; some of these people may be highly (and, at times, inappropriately) motivated to assume substantial risk without any expectation of direct health-related benefit.

Those having the authority to determine the appropriateness of research proposals should scrutinize with particular care those proposals which might involve subjects with limited capacities to consent, subjects existing in in-

herently coercible relationships to the investigators, and other subjects who have been identified as vulnerable. In general, one should be particularly concerned that the process of recruiting subjects does not even inadvertently capitalize on their vulnerabilities. The paper on guidelines for selection of subjects will address these problems in detail.

In consideration of benefit, is there any means by which individuals who are most likely to be benefited might be identified? If so, will these means be used to assist in recruiting research subjects who are most likely to be benefited? A necessary consequence of using such means is the exclusion of those who are relatively less likely to receive benefit. Thus, in the development of a therapeutic innovation--particularly one designed to alleviate a serious disorder or one whose administration or implementation entails consequential risk--it is generally most appropriate to select subjects in whom standard modalities have been tried without success.

Who has the authority or responsibility to assess risk-benefit criteria in the determination of the appropriateness of research?

For an extremely thorough survey of this issue the reader is referred to Katz, J.: Experimentation with Human Beings, Russell Sage Foundation, New York, 1972.

A central role should be assigned to the IRB in the assessment of risk-benefit criteria. A more thorough description of the IRB--its structure and functions--will be the subject of another paper. The following discussion will briefly outline how the IRB can discharge this particular responsibility, how it might analyze risk-benefit criteria differently in relation to different

sorts of research and subjects, and how the authority of the IRB is, or ought to be, limited in some cases and, in other cases, extended.

Limitations and extensions of IRB authority

In relation to research supported by DHEW it is now accepted that some aspects of IRB activity will be subject to review at a national level. Thus, for example, while the IRB will make determinations regarding the scientific merit of a proposal, the competency of the investigators, and the facilities available to them, this review will be repeated by appropriate study sections at NIH. Similarly, decisions regarding economic priorities--that is, which among all the approved research proposals will be funded--will similarly be made at a national level by study sections and advisory councils to the various institutes.

Some categories of research will also be reviewed at a national level with the focus of review being on the ethical aspects of the research. In its report

Research on the Fetus, the Commission recommended review by a national ethical review body for two categories of research on the fetus. In the rules and regulations promulgated by the Secretary, DHEW, following the receipt of the Commission's recommendations (August 8, 1975) national ethical review bodies named Ethical Advisory Boards were established. They are assigned responsibility for reviewing research on the fetus in the two categories specified by the Commission in its recommendations. Additionally, they are assigned responsibility for review of all proposed research involving in vitro fertilization. Thus, it appears that national ethical review will be focused on those sorts of activities classified as social risks to society; activities that might erode our concepts

of personhood or our assumptions of trusting relationships with one another.

Two other types of activity might appropriately be reviewed at a national level. The first is that sort of activity in which society is the subject and the risks to society are deemed substantial (in contrast to minimal as defined earlier by the Commission). The second type of research that one might wish to have reviewed at a national level is that in which the risks might be borne by subsequent generations. Thus, one might include in this category research and development procedures that might lead to pollution (broadly defined) of the environment or to genetically determined anomalies.

In most institutions having IRBs constructed as prescribed in DHEW rules and regulations, the IRB is assigned responsibility for review of all research--not only that conducted or supported by DHEW. It is also clear that most funding agencies now require "institutional endorsement" indicating that a research proposal has been reviewed by the IRB; these agencies include private foundations, drug industry, and others. It seems safe to assert that these agencies, like DHEW, have mechanisms analagous to those of DHEW for making determinations of scientific merit and economic priority.

Role of the IRB

With regard to assessment of risk-benefit criteria it is the responsibility of the IRB to review research protocols prepared by investigators. The IRB should first determine whether there are, in fact, any risks to the subjects or to society. If there are no material risks there is probably no need for further review.

If the IRB determines that there are risks it should proceed as follows: It should determine that the investigator has designed the protocol so as to minimize risk and maximize the chance of benefit. It should then attempt to determine whether: "The risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained

as to warrant a decision to allow the subject to accept these risks." The assumptions contained in this statement will be discussed in some detail in the next section.

In making this determination, the IRB will be obliged to consider the characteristics of the proposed subject population. In particular, is it proposed to recruit research subjects from populations that either have limited capacities to consent, have subordinate (inherently coercible) relationships to the investigator or his institution, or--for various other reasons--have been identified as especially vulnerable (supra)? In general, when such subjects are to be used there will be a requirement for lower risk-benefit ratios than in research proposing to use other sorts of subjects. Further, there will, in general, be a requirement that the hoped for benefits be, to the extent possible, direct health related benefits (to the subject) rather than other categories of benefits; in these subjects benefits that have been categorized as psychosocial, economic, and derivative, might be seen more as potential coercions than as hoped for benefits. Finally, IRB review should determine whether the hoped for benefit (knowledge) might be obtained if the research were conducted in less limited, coercible, or otherwise vulnerable populations; if so, use of vulnerable subjects should be avoided (cf, next section).

Having made the determination called for in the above cited quotation from DHEW regulations, the IRB should next review the plans for the consent negotiation. With regard to risks and benefits these will ordinarily be described on a consent form. The IRB should determine that there is an adequate description of risks and benefits (as broadly defined in this paper) to permit the prospective consentor to make a rational decision.

The role of the subject

Are we to consider the role of the subject to be a right to which all

citizens are entitled unless they are deprived of this right by due process of law? Alternatively, are we to consider it a responsibility which all citizens must assume when called upon? Alternatively, we might consider it neither; it might, for example, be considered a job for which one must be compensated appropriately. In the latter case appropriate compensation might be any of those compensations described in the section on benefits to the individual subject.

In considering this issue we may assume that agreement exists that it is in the interest of society to conduct research designed to improve the health, education, and welfare of its members and that most of this research cannot be conducted without human subjects. Thus, it is in the interest of society to have individuals who will assume the role of experimental subject.

Most roles that are valued by society are seen as either rights, responsibilities, or jobs. Obviously, these categories are not exclusive. In fact, most roles that we value are seen as jobs which any individual has the right to perform provided he has the qualifications and has not been deprived of that right by due process of law. Depending upon the outcome of these deliberations we may find ourselves presented with some novel additional questions. For example, as we consider developing guidelines for protection of individuals who--in our view--have limited capacities to consent--we must also consider the possibility that we are depriving such individuals of what they might consider their rights. To the extent we consider the role of subject as a job, we should decrease our concern with what sorts of benefits or rewards are permissible. Perhaps we should consider allowing the rewards to be determined--to some extent--by customary market factors.

In the framework of our current societal practices and customs it is relatively easy to view the role of subject as a right which in some cases may also be a job. The possibility that in some circumstances it might be ad-

vantageous to consider it a duty--as we have considered military service-- may be less apparent. This possibility and its implications--particularly in relation to research on children--has been discussed in detail in a provocative paper by Alexander Capron (Clinical Research. 21: 141-150, 1973)

Another fundamental question that must be asked can, perhaps, be disassociated from the analysis of the role of the research subject generally. Can an individual who is fully (materially) informed and reasonably free to make choices decide--for whatever reasons he considers appropriate--to participate in research that offers little or no direct benefit to him even though there is a considerable amount of personal risk? If the answer to this question is yes, the role of the IRB in relation to risk-benefit analysis would be limited to assuring that there is appropriate disclosure of risks and benefits and so on. In other words, in dealing with such prospective research subjects, the IRB would not be empowered "...to allow (or disallow) the subject to accept these risks". A particularly provocative consideration of the ramifications of a positive answer to this question is presented as The Case of the Kamikaze Astronauts (Katz, pp. 175-176).

3

THE NATURE AND DEFINITION OF INFORMED CONSENT
IN VARIOUS RESEARCH SETTINGS

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The Commission is charged with the responsibility to consider."

"The nature and definition of informed consent in various research settings." This paper is an attempt to identify and to begin to analyze the issues that must be considered as one attempts to respond to this charge. The following assumptions limit the scope of this paper: It is assumed that the reader will be familiar with the concepts developed in two previous papers prepared by the author for the Commission (1,2); this paper contains many references to the two previous papers. Separate papers are being developed for the Commission on research involving children, prisoners, the institutionalized mentally infirm and psychosurgery. Since it is assumed that these papers will deal with the nature and definition of informed consent in these sorts of subjects having limited capacities to consent, this paper will not address problems peculiar to those populations. Further, a separate paper: "...shall consider the appropriateness of applying (these) principles and guidelines...to the delivery of health services to patients under programs conducted or supported by the Secretary."

The paper begins with an identification of the various functions informed consent is meant to serve. The remainder of the paper is organized in two large sections. In the first there is an attempt to define informed consent and to analyze its various component processes. Barriers to the achievement of each of the component processes are also discussed. The objective of this part of the paper is to provide a definition of informed consent sufficiently comprehensive to cover almost all contingencies that might be encountered in negotiating for informed consent to various types

of biomedical, behavioral, and social research and with various types of subjects excluding those identified specifically above.

The next major section of the paper is concerned with various procedures that might be used to assure that informed consent has been achieved and, further, that it continues to be maintained during the conduct of the research activity. There is also a discussion of the various procedures, devices, and personnel that might be used to document the existence of informed consent and some conditions under which documentation of informed consent might be either unnecessary or detrimental to the interests of all concerned.

The functions of informed consent

Katz and Capron have enumerated several functions of informed consent (3 at pp. 82 et seq) to therapy (innovative as well as standard and accepted) for catastrophic diseases. However, the authors contend that--at least in catastrophic diseases--informed consent need not necessarily differ qualitatively as a function of whether the proposed therapy is innovative or accepted. Further, the functions are similar to those of informed consent to research identified earlier by the same authors (4).

The functions of informed consent are (3):

"a) To promote individual autonomy."

"b) To protect the patient-subject's status as a human being." On superficial examination it might appear that this category does not differ substantially from function "a". However, Katz and Capron see this as going far beyond the requirement for autonomy. A prospective subject may exercise

his autonomy by either agreeing or refusing to agree to assume the role of subject. If one would protect a subject's status as a human being one assumes the responsibility to attempt to create a true "joint enterprise" or partnership between the physician-investigator on one hand and, on the other, the patient-subject.

"c) To avoid fraud and duress."

"d) To encourage self-scrutiny by the physician-investigator."

"e) To encourage rational decisionmaking."

"f) To involve the public." The meaning of this particular purpose or function may not seem apparent without some elaboration.

"Primarily, the obtaining of consent can be important for the public relations of a physician or a medical center. The reverse is certainly true: A physician who develops the reputation of using his patients as guinea pigs for his studies or medical innovations without their informed consent will be avoided by those who know that reputation.

"Informed consent may also function beyond the area of public reputation and serve to increase society's awareness about human research."

In the preceding sentence, Katz and Capron are addressing particularly the practice of educating the public through mass media about all aspects of research involving human subjects. As they see it, part of the motivation for such informational campaigns might be to recruit individual subjects. However, it also results in making the general public a more informed decision maker in several respects. This function of informed consent will not be addressed further in this paper.

Another function of informed consent mentioned in this book but not designated as a separate category is identified here as:

g) To reduce the civil and/or criminal liability of the investigator

and his institution. Since a separate paper on the legal aspects of informed consent is being prepared for the Commission, this paper will deal with this function of informed consent only to a very limited extent.

Definitions of key words

The definitions of the key words to be used in this paper are those contained in Webster's Third New International Dictionary. Since not all of the definitions contained in that dictionary are germane to the present discussion, the following is a clarification of which definitions are to be used.

Informed, adjective: "1: Having information: based on possession of information."

The second definition of the adjective, informed, equates it with such words as educated, intelligent, and cultivated; thus, examples are given such as cultivated taste and educated opinion.

The first definition is the one to be used in this paper. The second definition develops the nuances of what one should be striving for as one attempts to create a condition that may be defined as informed consent. It is not merely having some information; it is striving for a situation in which the prospective consentor may be said to be educated or cultivated with respect to the proposition to which he might consent.

Information, noun: "1d: the communication or reception of knowledge or intelligence;" "2b: knowledge of a particular event or situation (synonyms: intelligence, news, advices);" "5: the process by which the form of an object of knowledge is impressed upon the apprehending mind so as to bring about the state of knowing."

Inform, verb transitive: "6: to communicate knowledge to: make ac-

quainted (synonyms: tell, advise, enlighten)."

Inform will also be used as an intransitive verb: "1: to give information: impart knowledge (synonyms: acquaint, apprise, advise, notify, advertise)." "These verbs signify to make aware or cognizant (of something). Inform implies the imparting of knowledge, especially of facts or events necessary to the understanding of a pertinent matter."

The various verbs listed as synonyms each have importantly different connotations. The distinctions are developed well in the cited dictionary. Since each has connotations different from those intended for the verb inform as used in this paper, none will be used. Further, the identification of these five verbs as synonyms has its roots in other definitions of the verb, inform, which are contained in the dictionary but not repeated in this section.

Consent: This word will be used both as a verb and as a noun. The full dimensions of the meaning of this word may be illustrated by pointing out that--whether used as a verb or a noun--it is derived from the Latin verb, consentire, meaning to feel together as well as to agree. Thus, among the now archaic or obsolete definitions of the word are: as a verb, to be in harmony or concord especially in opinion, statement, or sentiment. And as a noun, the being of one mind.

The definitions of consent to be used in this paper are as follows:

Noun, "1a: compliance or approval especially of what is done or proposed by another (synonyms, acquiescence, permission)" "b: capable, deliberate, and voluntary agreement to or concurrence in some act or purpose implying physical and mental power and free action--distinguished from assent." "3: agreement among persons usually as to a course of action or concerning a particular point of view or opinion."

Intransitive verb. "2: to express a willingness (as to accept a proposition or carry out a particular action): give assent or approval (synonym:

agree)."

Assent, noun: "1c: concurrence with approval (sanction)"; "3: agreement with a statement or proposal especially in a matter of minor importance or one detached from personal concern: mere acquiescence--distinguished from consent."

Assent, intransitive verb: "1: to give or express one's concurrence, acquiescence, or compliance (synonym: consent)." Among the various synonyms given for the verb, assent, are consent, accede, acquiesce, agree, and subscribe. "Assent indicates a concurring, either a positive agreeing or more passive conceding, without expressed doubts or objections. Consent indicates a complying, granting, or yielding, willing or reluctant, to request or demand."

It is of interest that the verbs assent and consent may be used as synonyms; assent seems to have connotations more of acquiescence; consent, on the other hand, seems to be a more positive action more closely approximating subscription than acquiescence. The differences in the nuances of the two words are developed more thoroughly when they are used as nouns. Thus, one definition of each is dependent upon its distinction from the other. Consent is much more a manifestation of the will of the consentor; it is much more an act of endorsement of an agreement. Assent, on the other hand, may be a manifestation of a relative lack of interest.

Definitions of informed consent

According to Katz (4 at p. 523): "...the concept of informed consent has been accepted in case and commentary as a cardinal principle for judging the propriety of research with human beings. Yet law has neither defined sufficiently well the substance and ambit of informed consent in therapeutic settings nor determined clearly its functional relevance for human experimentation. Thus, in invoking informed consent like a talisman, lawyers, investigators, and courts often seem to overlook the fact that it lacks specific construction and remains an ill-defined concept."

Further (4 at p. 521): "Belief in the idea of individual freedom is a cornerstone of the Western concept of man and society. The common law nurtures and protects individual freedom through the doctrine of self-determin-

ation, which confers on each person the right to pursue his own ends in his own way so long as he does not interfere with specified rights of other individuals or of the community. The requirement of consent is the primary means for implementing the abstract notion of self-determination. Tort law, for example, guards a man's property and person against interferences to which he has not consented. Similarly, a contract comes into being when two or more persons agree with each other that certain terms should govern their relationship.

"In most commercial transactions, each party is responsible for informing himself about the terms and implications of the contract. However, when professionals intervene in the lives of others, a higher standard is imposed upon them. They may be held responsible not only for obtaining the layman's consent, but also for informing him of the consequences of their agreement."

Thus, it may be concluded that informed consent is a type of contract in which one of the contractors (the investigator)--as in all fiduciary relationships--is held accountable for higher standards of responsible conduct than are most individuals in creating commercial contracts. Further, it is clear that the precise definition and nature of informed consent have not yet been established.

DHEW rules and regulations (5) provide a definition of informed consent which includes a specification of its 6 basic elements:

"46.3(c) "Informed consent" means the knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion. The basic elements of information necessary to such consent include:

- (1) A fair explanation of the procedures to be followed, and their purposes, including identification of any procedures which are experimental;
- (2) a description of any attendant discomforts and risks reasonably to be expected;
- (3) a description of any benefits reasonably to be expected;
- (4) a disclosure of any appropriate alternative procedures that might be advantageous for the subject;

(5) an offer to answer any inquiries concerning the procedures; and

(6) an instruction that the person is free to withdraw his consent and to discontinue participation in the project or activity at any time without prejudice to the subject."

Components of informed consent

The process of creating a condition that may be called informed consent is commonly seen simplistically as one having two components. The first component is that of informing--the transmission of information from the investigator to the prospective subject. The second component is that of consenting; this is signified by a declaration on the part of the prospective subject that he has assimilated the information and that he is willing to assume the role of subject. Even more simplistically, it may be assumed that these two components are accomplished sequentially; ie, after the information is transmitted the individual consents or refuses to consent. DHEW regulations recognize that there may be some disruption in the sequence of these processes by requiring "(5) an offer to answer any inquiries concerning the procedures...". Katz (6 at p. 786) proposes an entirely different way of viewing the process. He sees the process as essentially an invitation offered by the investigator to the prospective subject to join him as a partner in a collaborative venture:

"Informed consent--would entail, if it is truly seen as an invitation, asking for consent, seeking authorization to proceed, and not making a demand under the guise of a symbolic egalitarian gesture. It would necessitate sharing knowledge and admitting ignorance, answering questions and identifying unanswerable questions, appreciating doubts and respecting fears...It requires that the interaction between investigator and subject become a partnership, giving the subject the right to determine what should be done for and with him, and forcing the investigator to be explicit in what he wants to do and why. Thus the controversy over the subject's capacity and incapacity to understand, on which the debate about informed consent has focused, is a displace-

ment from the real issue, which is the dread of an open and searching dialogue between the investigator and his subject. This displacement is caused by the unacknowledged anxiety over making the invitation in the first place."

As individuals communicate with each other toward the goal of achieving a condition (a special type of contract) designated informed consent, each of the component processes may occur in any order. It is proposed that the most appropriate single word that may be used to refer to the total communications is negotiation. Thus the total process will often be referred to as negotiating informed consent. Many documents use different words to name this process. Thus investigators are often admonished or advised to secure or to obtain informed consent. Such words as secure or obtain do not capture the full dimensions of the desired interactions; viz, an interaction involving dialogue, encounter and so on. For purposes of this discussion, the negotiations will be discussed as having four separate component parts. 1) Informing; 2) assessment of the prospective consentor's comprehension; 3) assessment of the prospective consentor's autonomy; and 4) consent. Negotiations for informed consent in the real world never are conducted as four separate component processes.

Informing

In this section the types of information that should be communicated to the prospective consentor will be identified. There will be eleven essential elements of information, six of which correspond to those identified in DHEW regulations.

1) There should be a clear statement of the overall purpose of the research. When appropriate, it should be stated that there is not only

an immediate purpose but also a larger ultimate purpose. Thus, for example, it might be stated that the immediate purpose of this research is to develop a more sophisticated understanding of normal kidney function. If the immediate purpose is achieved, one hopes that this information might contribute to our ability to identify and treat persons with diseases of the kidney.

One of the most important consequences of stating the purpose of the research is that it might alert the prospective subject to decline participation in research the goals of which he does not share. Thus, for example, some individuals might not wish to contribute to the general fund of information that would enhance our capacities for genetic modelling. Some others may decline to participate in research that might identify their racial or ethnic group as having certain qualities; eg, as having lower intelligence than the general population.

This element of information may partially duplicate number 6 (infra). In some situations it might be appropriate to not reveal the true purpose of the research (number 11).

2) There should be a clear invitation (not a request or a demand) to the individual to become a research subject. The implications of playing the role of subject--as opposed to any alternative role available to the individual--should be clearly indicated. Most importantly, when one agrees to play the role of subject, one ordinarily agrees to become--at least to some extent--a means to an end (1 at p. 3).

If the research is of the sort classified as innovative therapy, the physician-investigator may be held liable for failure to obtain informed consent merely by virtue of having failed to explain that the procedure

used represented a departure from customary practice (7 at p. 253).

3) The prospective subject should be informed as to why he has been selected for participation in the research. Ordinarily this is because of some specific disease (or other life situation) that he or one of his relatives might have. In other cases it might be that the investigator presumes that he does not have that disease or condition; it might be that he is being asked to serve as a control in studies designed to explore that condition.

In some cases, the first approach to a prospective research subject might involve some sorts of testing to determine if he is in fact eligible to be a subject of the proposed research. The performance of diagnostic or other testing solely for purposes of identifying an experimental subject population is itself a form of research. In these situations it is essential to negotiate informed consent to undertake the "pre-screening" procedures. This negotiation should of itself contain all eleven elements of informing that are appropriate; in addition, the consequences of being found eligible for participation in the research project should be made clear. Thus, as one is negotiating informed consent to participate in pre-screening tests, one should also inform the prospective subject as to what research he will be invited to participate in if he "passes" the pre-screening tests. Some of the consequences peculiar to "failure to pass pre-screening tests" have been detailed earlier (2 at p. 9).

4) There should be: "A fair explanation of the procedures to be followed, and their purposes, including an identification of any procedures

which are experimental." (5, Section 46.3(c)(1). A fair explanation would include identification of all procedures and interactions that would be of material interest to the prospective subject. Thus, if it is proposed to draw a small amount of blood from a vein for purposes of assaying some chemical, the prospective subject might be expected to be more interested in knowing how much blood will be drawn, how often it might be repeated, where he might have to go to have the procedure done, and what practical consequences to him there might be of the results of the assay than he would in the details of the assay technique. Further, he might be interested in who (if not the individual negotiating the consent) might draw the blood and what his experience and qualifications are. The language necessary to convey the meaning of each of these bits of information will obviously vary enormously depending upon the experience of the prospective subject with previous drawings of blood. Thus, for example, it might be possible to relate the amount of blood to be drawn in terms of what fraction it is of the amount removed when one donates a pint of blood or in relation to the amount the individual has had drawn for various diagnostic tests in the past.

Thus, in addition to describing each of the experimental procedures-- particularly as they affect the prospective subject--it is ordinarily advisable to anticipate that the prospective subject will want to know: a) With whom shall I interact? b) Where will the research be done? c) When will the research be done? d) How often will the various procedures be

performed? e) How much of my time will be involved?

a) Most prospective subjects will be reassured to learn that the individual negotiating for informed consent with him will play a key role in the actual conduct of the research (cf, who shall negotiate with the prospective subject?). However, many types of research activities require interaction with a large number and variety of professionals and their assistants. In general, it is better to advise the prospective subject of the numbers and types of individuals with whom he will interact rather than to surprise him during the course of the research. Thus, for example, some prospective subjects may have strong biases against physical examinations by individuals of the opposite sex or by students.

b) For various reasons prospective subjects will be interested in where the research is to be conducted. Thus, for example, some might feel reassured to learn that a questionnaire will be administered in their own homes; others might regard this as an unwelcome intrusion. In some cases--eg, in some hospitals--the research unit might be more or less attractive to the prospective subject than the alternative facilities he might have to use should he choose the role of patient. A statement of where the research is to be done will also allow the prospective subject to assess the amount of inconvenience there might be in traveling to and from that location.

c) An explanation of when the research is to be done will allow the prospective subject to determine whether there are any essential time conflicts with his own schedule. Some sorts of research are dependent upon repeating observations at precisely timed intervals. If this is discussed

frankly at the outset it may be possible to negotiate a mutually satisfactory schedule; alternatively, it may be found that a subject must drop out during the course of the research owing to a prior commitment.

d) A precise statement as to how often various procedures will be performed will also assist the subject in assessing the totality of his personal commitment of time and other inconvenience. In some research, it is necessary to have various follow-up procedures done at intervals as long as a year or more. If the prospective subject knows he will not be available that much later--because, perhaps, he might be leaving the country--he can advise the investigator that his full participation will be impossible.

e) In explaining how long the research will take there should be an estimate not only of how much time each component of the research may reasonably be expected to occupy but also of the total duration of the research.

In complicated research activities it is occasionally of value to invite the prospective subject to visit the site of the proposed research (eg, the metabolic research unit, the office of the investigator, the physiology laboratory) where he might see the personnel, facilities, apparatus, and so on, that will be involved. Many types of biomedical, behavioral, and social research are conducted as components of what has been identified previously as complex activities (1 at p. 9). In these cases special care should be given to explaining which of the activities are done exclusively for research purposes. In these situations, the bits of information identified as a) through e) should be elaborated

as follows: If you agree to participate in this research you will be interacting with (specify) additional types of individuals; it will take (specify) additional time; procedures that might have been done n times will be repeated n plus x times; the location will change in a specified way; and so on.

5) There should be: "A description of any attendant discomforts and risks reasonably to be expected" (5, Section 46.3(c)(2)). This quotation from DHEW regulations requires some elaboration. Under the rubric of discomforts one should include not only physical and psychological discomforts but also personal inconveniences. The sorts of personal inconveniences that might be expected to occur as a consequence of participating in research were discussed in the preceding section. The prospective subject should be advised that many research procedures might produce a variety of physical or psychological discomforts. Thus, for example, a naive subject might assume that a spinal tap would produce some pain by virtue of a needle being inserted low in his back. On the other hand, it may not be assumed that he will understand that there is a high probability of a headache which might be quite severe following the procedure. A person who is being asked to have skin tests for certain allergies should be advised that if the tests are positive they might itch, produce transient discoloration or other disfigurement, and so on. A person being asked to complete a questionnaire should be advised, if appropriate, that he is likely to find some of the questions either irritating or embarrassing.

The risks of participation in research have been categorized in an earlier paper (2). The various physical, psychological, social, legal, and economic risks to the subject should be identified during the process of informing. An adequate description of each risk has also been identified in the same paper; to the extent possible (or necessary) each risk should be expressed clearly in terms of its probability and its magnitude (2 at p. 49). A clear statement should be made as to what steps will be taken to assure the early detection, minimization, and/or correction of various harms. There should be clear statements as to how the prospective subject will (or will not) be compensated for whatever harms occur. Legal barriers (if any) to preservation of confidentiality should be discussed candidly.

In some cases the prospective subject will be called upon to assume responsibility for minimizing the chance of harm. He will be asked to perform certain functions during the course of the research to accomplish this objective. For example, when a woman of childbearing age participates in a research activity in which there is known or unknown risk to the fetus, she should be advised that if she wishes to be a subject she should avoid becoming pregnant. Her plans for avoiding conception should be reviewed during the consent negotiations. At times, if her plans seem inadequate, it will be necessary to either exclude her from the research or to ask her to agree to more certain plans for contraception. She should further be advised that if, during the course of the research, she deviates from the plans discussed at the outset, she should advise the investigator immediately.

Another common problem is presented in negotiations for informed con-

sent to "double-blind" drug trials.

It must be made clear that neither the investigator nor the subject will know what drugs the subject is taking. This may present a problem if the subject becomes ill and requires emergency treatment. The physician who is called upon to administer treatment in an emergency may find that he is unable to plan such therapy rationally without knowing exactly what drugs the subject (now become patient) is taking. Thus, the subject should be advised that he will be provided with a card indicating that he is a subject of a "double-blind" drug trial; the card should also include the subject's code number in the trial. Further, on this card there should be a telephone number at which there will be someone on 24 hour call who has access to the codes for the study. Thus, in the event that a physician must know immediately what drugs the subject is taking, he will be assured immediate access to this information at any time. The subject should be advised of the importance of keeping this card with him at all times.

Must all risks be fully disclosed? If not, how does one determine which must?

There are distinct perils to the process of informed consent presented by overdisclosure and by underdisclosure. Some of the perils of overdisclosure were documented by Epstein and Lasagna (8). They presented consent forms of various lengths and thoroughnesses to prospective subjects of a drug study. They found that the more detail was included the more likely were the prospective subjects to be either confused or intimi-

dated. In their study they found a remarkably high incidence of refusal to take an experimental drug based upon its apparent danger. At the conclusion of the study they informed the individuals who refused that the drug they were describing--the drug they refused to accept money for taking--was aspirin; many of those who refused were regular users of aspirin. Almost all of them reported that although they had declined participation in the "study", they intended to continue to use aspirin essentially as they had before.

In the medical practice context, a study was done to determine the influence of full disclosure on the willingness of patients to consent to angiography (9). The publication of the results of this study includes the consent forms and questionnaires used. The consent forms seem to contain an adequate description of the risks of the procedure (a small probability of serious complications which might include death). In understanding the implications of this study it is important to know that, since angiography is a diagnostic procedure, its performance may or may not result in any information upon which further therapy might be recommended. Of 232 patients asked to consent, all but 2 per cent did. Response to the questionnaire indicated that the majority of patients were pleased to have the information conveyed in the consent form. The author concludes that he is convinced of the value of disclosure to the extent contained on their form.

Under informing, on the other hand, may be perilous to all participants in the research process. Inadequately informed subjects may make

wrong choices. Harmed subjects who had not been informed of the possibility of that particular harm might quite appropriately litigate against the investigator.

Perhaps the ideal for which one should strive is a "materially" informed subject. One definition of material risk is provided in a decision of the District of Columbia Court of Appeals in 1972 (10). In this case the court held that the disclosure required was determined by the "patient's right of self-decision" and further that the patient's right to make his own decision can be termed "effectively exercised only if the patient possesses enough information to enable an intelligent choice."...A risk is thus material when a reasonable person, in what the physician knows or should know to be the patient's position, would be likely to attach significance to the risks or cluster of risks in deciding whether or not to forego the proposed therapy." This definition might be applied to determining materiality of risk in the research context by changing the words patient, physician and therapy, to subject, investigator, and research, respectively.

One problem with this definition of materiality is that it puts the particular physician or investigator in the precarious position of having to know in advance what harms a particular patient or subject might consider material after they occur. As the court noted in Cobbs v. Grant (11): "Since at the time of trial the uncommunicated hazard has materialized, it would be surprising if the patient-plaintiff did not claim that had he been informed of the dangers he would have declined treatment.

Subjectively he may believe so with the 20-20 vision of hindsight, but we doubt that justice will be served by placing the physician in jeopardy of the patient's bitterness and disillusionment". Thus, some courts have held that in determining issues of materiality of risk, one should adhere to the reasonable person or "prudent-patient test." How does one determine what the reasonable person or "prudent prospective subject" might wish to know? In the context of research such decisions are largely made by the IRB. The IRB reviews a research protocol and determines the minimum standards for disclosure of risk in the consent negotiation with prospective subjects. However, the capability of the IRB to perform this function has been challenged by some commentators. In particular it is suggested that since the IRB is dominated by scientists it does not truly reflect the needs of the reasonable lay-person to know.

Various remedies for this situation have been proposed. Two of the most extreme are the following:

Hauck (12) has proposed that a "consent jury" be appointed--much like a trial jury--from the ranks of non-scientists. He further proposes that all the risks of each experiment be listed by those having the scientific expertise to do so--perhaps an IRB. Then, using an adversary system, the materiality of each risk would be debated before the jury. Each risk would have an expert advocate for its disclosure and an expert advocate for its non-disclosure. At the conclusion of the debate the jury would determine which risks should be disclosed and in what fashion. Two faults of this procedure should be mentioned. Firstly, like any other system, it assumes

an average subject; it permits no flexibility on the part of the individual who is negotiating informed consent to provide more or less disclosure dependent upon the needs of a particular prospective subject. Secondly, this process would consume enormous amounts of time and energy.

Norman Fost (23) has proposed that a "surrogate system" might be used to achieve the same sorts of purposes (as well as others) Hauck proposes for the "consent jury". Fost suggests that the surrogates be selected from a population that matches as closely as possible that from which prospective subjects might be drawn in all respects but one: They should be aware that--for some reason--they are not eligible to become subjects (although they are asked to pretend that they are). His proposal differs from Hauck's in that the surrogates would not meet as a group; rather they would meet as individuals with the investigator. The surrogate system is designed to inform the negotiator for informed consent of the range and diversity of factors of material interest to individuals similar to prospective subjects. Fost emphasizes that he is not proposing this system as a necessary adjunct to the approval of research proposals (emphasis in the original).

A second extreme remedy has been proposed by DHEW (13, 14). They propose that Consent Committees should be established to monitor the actual process of negotiating informed consent with persons having "limited capacities to consent". This process permits flexibility in that it permits responsiveness to the needs of a particular prospective subject. However, it shares with Hauck's proposal the fact that it would be enormously cumbersome (cf, Consent Committees).

6) There should be: "A description of any benefits reasonably to be expected," (5, Section 46.3(c)(3)). The types of benefits that might be described have been categorized earlier as: a) Direct health benefits; b) Psychosocial benefits; c) Economic benefits; and d) Derivative benefits (2 at p. 29). In most consent negotiations there should be--when appropriate--a thorough disclosure of categories a) and c). Whether or not it is appropriate to mention categories b) and d) and the extent to which they might be emphasized will often be controversial. Similarly, the emphasis that ought to be given to societal benefits in the consent negotiations will also be controversial. In general, these controversies should be resolved by the IRB. The main determination they must make will be based on their judgment of the effects of mentioning such benefits to the specific proposed research subject population. They must determine the extent to which that specific population might be unduly coerced by the offering--implicit or explicit--of such benefits.

a) Direct health benefits. Hoped for benefits that might be discussed quite analogously to direct health benefits would include direct educational benefits, direct welfare benefits, improved working conditions, and so on. The optimal description of a hoped for benefit has been detailed in an earlier paper (2 at p. 49). It should be emphasized that it is a hoped for benefit--not something that can be guaranteed. Particularly in the category of innovative therapy (innovative practices) it should be emphasized that, while a major purpose is to attempt to bring direct benefit to the subject, an additional purpose is to try to develop a systematic body

of new knowledge. Thus, the prospective subject is not the only intended beneficiary of the activities. Additionally, as a consequence of this dual purpose, it will ordinarily be necessary to do additional procedures--more testing and more monitoring--than would be necessary were the individual playing exclusively the role of patient, student, and so on. As discussed earlier (2), to the extent possible, each hoped for benefit should be assessed in terms of its probability and potential magnitude (including, when appropriate, its expected duration).

c) There should be a clear statement of any material inducements that are offered to the prospective subject in exchange for his participation. Such inducements might include cash, food, clothing, improved accommodations, and so on. If the material reward is contingent upon completion of the project--that is, if the subject will lose all or part of the reward as a consequence of withdrawal from the project--this should be specified.

7) There should be: "A disclosure of any appropriate alternative procedures that might be advantageous for the (prospective) subject" (5, Section 46.3(c)(4)). The alternatives in general to playing the role of subject will be discussed in detail below (number 10). In this section there will be a more narrow focus on research activities in which the hoped for outcome is to bring a direct health related benefit to the prospective subject. To some extent, the concepts elaborated in this section might also be applied to research in education and welfare and in some sorts of social research in which there is similarly a hoped for outcome of direct benefit to the prospective subject. In general, the

model for this type of research is that defined as innovative therapy (innovative practices) (1, at p. 9a).

If it is being proposed that the prospective subject consent to some therapeutic innovation, there should also be at least a disclosure of what other therapies are available for his condition; this should include a statement of those that are accepted and approved as well as others that might be considered innovative. In order to facilitate rational decision making there should be a reasonable statement of the risks and benefits of the alternative therapies. Occasionally, this will demand a frank statement that the risks and benefits of the proposed innovation are relatively less known than are those of the accepted or approved alternatives. Failure to disclose the existence of alternative therapies has been held to constitute malpractice (7, at p. 231).

In most cases, if the therapeutic innovation fails it will be possible to revert to standard and accepted therapy for the same condition. However, some innovative therapies by their very nature preclude alternative therapies, if so, this should be disclosed. This possibility may present itself in a variety of situations; some examples follow:

In some diseases there is an ever-present possibility of the sudden occurrence of some permanent complication. Thus, during the course of experimentation with a new antihypertensive drug, it may be necessary to withhold known effective therapy. Should the new drug fail to control the blood pressure, the subject is liable to the sudden onset of a serious and

irreversible complication such as cerebral hemorrhage.

Some innovative therapies are designed to permanently ablate some tissue or organ by either surgery or radiation. Should the therapy fail, the tissue or organ remains ablated usually with corresponding permanent loss of function. An innovative program to assist children in overcoming reading disabilities may prove ineffective. As a consequence, a crucial period in the child's development during which some other program might have had a more or less salutary effect, has been lost irrevocably.

8) There should be: "An offer to answer any inquiries concerning the procedures" (5, Section 46.3 (c)(5)). Mechanisms for insuring that the prospective subjects will have a maximum opportunity to have questions answered are discussed in several subsequent sections.

9) When appropriate there should be a suggestion to the prospective subject that he might wish to discuss the proposed research with another before consenting. In some situations, consent of another individual will be required by regulation; eg, non-therapeutic research directed at the fetus will require the informed consent of the father as well as the mother (15). In some other situations consultation with a third party (other than the investigator and prospective subject) will be either required or strongly suggested by the IRB. These situations will be discussed in detail below (cf, Consent Committee and Third Party Scrutiny). In some situations in which the proposed research entails a consequential amount of risk, discomfort, or inconvenience, to the prospective subject--or, in innovative therapy, when there are difficult choices between reasonable alternatives--

it should be suggested that he might wish either to consult with a trusted advisor or to share the burdens of decision-making with another.

Most commonly, the trusted advisor will be a "physician-friend". Ideally, this would be the prospective subject's personal physician who has no involvement in the research; even more ideally, this physician would have no affiliation with the institution in which the research is to be done. When the prospective subject has no personal physician or when the personal physician is involved in the conduct of the research, it might be appropriate to offer the services of another physician. In other cases, depending upon the nature of the research, it might be suggested that the prospective subject might wish to consult a trusted clergyman, lawyer, some other appropriate professional advisor, or a friend (who need not also be a professional).

In some situations the prospective subject might be advised to involve a third party in the decision-making process even though this is not required by law or by the IRB. Thus, for example, in studies on the efficacy of a new post-coital contraceptive: It should be made clear that since this is an experimental maneuver there is a real possibility that it might fail. The prospective subject should be advised that she might wish to have her coital partner involved in the negotiations for informed consent. This would be particularly true if her partner might subsequently be called upon to share the burdens of decision-making and/or financing on the issues of either abortion or carrying the pregnancy to term should the experimental drug prove ineffective. Of course, she might refuse to involve her partner in the decision. In this case, she should

be made aware of all of the potential burdens for which she has assumed independent responsibility.

Although the author is aware of no case in which a coital partner has been found not liable for support of a child born after failure of an experimental post-coital contraceptive, perhaps an analogy might be drawn from decisions regarding the outcome of artificial insemination (7, at p. 245). Thus, in the case of Gursky v. Gursky, it was found that a husband was not liable for the support of a child conceived by artificial insemination on grounds that he was not consulted and, therefore did not consent prior to the artificial insemination. This decision was rendered on the occasion of the divorce of the two litigants.

A somewhat--but not precisely--analogous situation is presented when a man is asked to consent to an experimental form of sterilization. For a variety of reasons, including those mentioned in the preceding paragraphs, it might be suggested to him that he might wish to share decision-making responsibilities with his mate. Some states, by statute, require spousal consent to sterilizations (7, at p. 30). However, even where such consent is not required by statute, the man with whom consent for an experimental approach to sterilization is being negotiated should be made aware of the potential consequences of not sharing the burden of decision-making responsibilities.

10) It should be stated that the prospective subject is free to refuse to participate in the research and further, that he is free to

withdraw from the research at any time. If the research, once commenced, precludes withdrawal this should be explicitly stated. Further, the prospective subject should be advised that such refusal or withdrawal will in no way adversely prejudice his future interactions with his physician (or other professional), with the investigator, or with the institution. Assurance that refusal or withdrawal will not adversely prejudice future interactions is especially required when any relationship exists between the investigator (or any colleague of the investigator) and the prospective subject which has any potential for coercion; such relationships include physician-patient; employer-employee; faculty-student; and so on. This element of information is an elaboration of section 46.3(c)(6) of DHEW regulations (5).

A particular concern here is that individuals who are voluntarily playing the role of patient, student, or employee, or who are applying to a professional or to an institution for one of those roles, not be deprived of their rights to enjoy all of the usual expectations of such roles as punishment for having refused to play the role of subject either in addition to or in place of the role they wish to play.

In some situations it may be impossible--or at least very difficult--to make the promises called for in the preceding paragraph. Thus, for some diseases the only definitive approach to therapy is innovative. For example, if a child with a growth defect wishes to receive human growth hormone (HGH) this can be given only to those who agree to participate in re-

search designed to test its safety and efficacy. HGH, which is in very short supply, and which is very expensive, is supplied only to investigators who agree to administer it according to a research protocol prescribed by the supplier. Thus, the offer to the parent of a child who requires HGH that he might refuse to participate in the research without adversely prejudicing his relationships to the physician-investigator would be rather vapid. Standard medical care in this situation would consist of watching the child fail to grow over the years.

A somewhat analogous situation is presented when the patient has a malignant tumor (or another inevitably lethal disease) for which all standard modes of therapy have been tried without success. The only definitive approach to therapy might be a therapeutic innovation. However, in this situation if the patient (prospective subject) refuses to consent to the research, he may at least be assured that he will continue to receive all the supportive, palliative, and symptomatic therapy at the physician's disposal.

When the therapeutic innovation involves a manipulation of the health delivery system (1, at p. 20) or the introduction of new types of health professionals (1, at p. 18) it may very often be the case that that particular institution can offer no alternative. Thus, for example, methadone maintenance programs may be obliged to state that as a pre-condition of participation in the program, the patient (subject) is obliged also to participate in some forms of research. Similarly, experimental clinics have been established to assist smokers to discontinue this habit; if the

smoker is unwilling to participate in the research there may be no alternative facility or service offered by the institution.

A rather novel example was presented by a proposal to video-tape the interactions of certain individuals on a psychiatric research ward. The individuals whom the investigators wished to study comprised approximately one-third of the total population of the ward. However, it was obvious to all concerned that the video-tapes would also record the activities of the other two-thirds of the research ward population (as well as the staff, visitors, and so on). Thus, in conducting negotiations for informed consent with the two-thirds who were not the intended subjects of the video-tape research, it was necessary to inform them that their continued participation in their own research projects would also involve video-taping of their activities. Those who objected to this did, in fact, have their relationships to the institution prejudiced. The only way they could escape was to discontinue their participation as research subjects in studies in which they wanted to be involved.

11) In some studies it is necessary to inform the prospective subject that some information is being withheld deliberately. This is particularly true in some types of behavioral and social research in which disclosure of the purpose of the studies would vitiate the validity of the results. Ordinarily in such studies it is required that the prospective subjects be informed of all aspects of the study other than its purpose. There should also be an offer to disclose the purpose at the conclusion of the study.

"Undisclosed purpose" research is not confined to the social sciences. Thus, for example, in biomedical research "patient compliance" studies are dependent for their success upon the agreement of the prospective subject to remain ignorant of the purpose until the conclusion of the study. In such cases, the IRB should demand assurance from the investigators that the information developed will not be used to embarrass, harass, or otherwise abuse any individuals who agree to participate. Thus, for example, it would be quite inappropriate at the end of such a study to confront a subject with such statements as: "Now we have caught you; you do not take your medicines" (patient compliance study). Or: "We have identified you as a sadist" (social research example). Rather, in general, during the "debriefing" the subjects should be informed that the study identified in general the prevalence of non-compliance or tendencies to cruelty.

In the view of the author, deliberate deception--lying to prospective subjects--should be avoided. The American Psychological Association indicates that in extraordinary circumstances, deliberate lying to prospective subjects might be justified (16, at p. 38).

Comprehension

Valid informed consent cannot exist unless the consentor comprehends the information upon which his consent is based. In the context of professional practice our legal system seems to be evolving the concept that the professional not only has the responsibility for informing a client as to what will be done but also has the responsibility for

seeing to it that the client understands the information (4, at p. 521). In the context of medical practice, informed consent has been found not to exist because patients have not understood such words as mastectomy (4, at p. 651), laminectomy (7, at p. 232), and so on. Similarly, patients have been judged to be uninformed owing to "limited command of the English language" (7, at p. 125). Also in Reyes v. Wyeth Laboratories (17) the fact that the plaintiff had "...a seventh grade education, but her primary language is Spanish"...was taken to imply that she may have "...lacked the linguistic ability to understand..." the significance of a form she had signed. Parenthetically, in the latter case, this was not a pivotal point since the form lacked the information that the court considered important. Such failures in communication can ordinarily be obviated by explaining technical procedures in lay terminology and by the use of interpreters and translators as necessary.

Incidentally, it should be noted that in some cases the patient or prospective subject might have a perfectly adequate command of the English language; the physician, however, may not. This is particularly a problem when foreign medical graduates are employed as interns, residents, or post-doctoral fellows. A recent article (18) cites several trial court cases in which hospitals were found liable for malpractice because--owing to inadequate command of the English language--a foreign medical graduate had either taken an inadequate history or failed to provide instructions to patients.

Additional steps may be taken by the investigator to assure himself

that the prospective subject comprehends the information. He might, for example, ask the prospective subject some questions about the proposed research. He might ask the prospective subject to explain some of the more important points of information in the subject's own words. It has been proposed by Miller and Willner (19) that in some research projects--particularly those in which there is a large amount of complex information presented to the prospective subject--that this process might be formalized in what they call the "two-part consent form". The first part of the two-part consent form is a standard consent form prepared for the research project. After the information has been presented to the prospective subject and after he has had the opportunity to have his questions answered, he is presented with the second part of the consent form. The second part consists of a brief quiz on the essential elements of information that have already been presented. The prospective subject is asked to respond in his own words to such questions as: How much time will you be spending in the hospital if you agree to participate in this research? How much time would you spend in the hospital if you do not participate in this research? Thus, through the second part of the consent form it might be documented that the prospective subject has a clear grasp not only of what he is consenting to but also of the consequences of his consent.

It has also been proposed that the consent committee might also contribute to the assurance that the prospective subject comprehends (cf, Consent Committees).

Autonomy

DHEW regulations (5) prescribe that a fundamental feature defining informed consent is that consentor be "...so situated as to be able to exercise free power of choice with undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion." Implicit in this clause is the requirement or expectation that the individual who is negotiating informed consent will somehow determine adequately that the prospective subject is suitably free to make the choices presented to him. In general, it will be relatively easy to avoid intentional fraud or deceit; similarly, it will ordinarily be easy to detect retrospectively situations in which fraud and deceit were used to secure informed consent. Obviously, in such cases there is no informed consent; rather, there is misinformed consent.

The other components of this requirement may be more difficult to achieve even by the most sincere negotiators for informed consent. Similarly, it may be most difficult to determine retrospectively whether a given subject has been inappropriately coerced or constrained.

It is possible to question whether any individual who perceives himself as a member of society is totally free to make choices regarding the disposition of his own body. In one way or another those who exercise their choices beyond the bounds of the expectations of their groups might be perceived as antisocial; they may be described by those who observe their behavior with adjectives ranging from eccentric to sociopathic.

Perhaps the most important category of prospective subject that must be considered is that of the patient or "sick person". To illustrate the barriers presented to the achievement of autonomy by having assumed the role of "sick person", let us examine Talcott Parsons' view of this role in relation to the physician (4, at p. 203). Parsons discusses the role of patient and physician in the context of his definition of health and the overall role of medicine in society. Health is defined in terms of a given individual's capacity to perform effectively the roles and tasks for which he has been socialized, and the concept of a person's health is integrally defined with respect to a person's participation in the social system.

Illness is also defined within the context of the social system and therefore, is judged as being indicative of a disturbance of the capacity to perform roles and tasks effectively. Parsons identifies four aspects of the institutionalized expectation system relative to the sick role:

1) There is an "...exemption from normal social role responsibilities, which of course is relative to the nature and severity of the illness. This exemption requires legitimation by and to the various alters involved and the physician often serves as a court of appeal as well as a direct legitimating agent...being sick enough to avoid obligations can not only be a right of the sick person but an obligation upon him...."

2) "...the sick person cannot be expected by "pulling himself together" to get well by an act of decision or will. In this sense also he is exempted from responsibility--he is in a condition that must "be taken care of." "...the process of recovery may be spontaneous but while the illness lasts he can't "help it". This element in the definition of the state of illness is crucial as a bridge to the acceptance of "help"."

3) "...the state of being ill is itself undesirable with its obligation to want to "get well." The first two elements of legitimation of the sick role thus are conditional in a highly important sense. It is a relative legitimation so long as he is in this unfortunate state which both he and alter hope he can get out of as expeditiously as possible."

4) There is an obligation upon the sick person "...to seek technically competent help, namely, in the most usual sense, that of a physician and to cooperate with him in the process of trying to get well. It is here, of course, that the role of the sick person as patient becomes articulated with that of the physician in a complementary role structure." (emphasis in the original).

Parsons describes in considerable detail the practical consequences of this definition of the sick role (20). The second component of the sick role may be perceived by the sick person as a type of personal gain. At least temporarily, he is relieved of various duties and obligations which he might consider onerous. However, this social definition of illness imposes upon the "responsible" sick person the obligation to seek and cooperate with competent help (ordinarily health professionals); if he fails in these responsibilities, his sick role will eventually come to be seen as illegitimate (irresponsible).

A second barrier to the achievement of autonomy is the assumption on the part of both the sick person and the health professional that the former--unless he is himself trained in the profession--has no possibility of achieving the degree of understanding that permits the latter to make health-related decisions relatively easily. Thus many studies have indicated that sick persons are likely to "go along with" the judgment of their physician without probing the bases for such judgments. On the other hand, many physicians have expressed exasperation and frustration with the prospect of being obliged to inform a patient to the extent that the latter can make a rational choice. An illustrative example of the intensity of such feelings is presented by P.J. Burnham as a model form for consent to

herniorrhaphy (4, at p. 658).

In reflecting on these and other limitations of the sick role Jonas (21) reached the tentative conclusion that as we consider who is eligible to be recruited ("conscripted") for the role of research subject: "Least and last of all the sick--the most available of all as they are under treatment and observation anyway." Yet, he recognizes that "...the very destination of medical research, the conquest of disease, requires at the crucial stage trial and verification on precisely the sufferers from the disease, and their total exemption would defeat the purpose itself." Thus, subsequently, he proposes: "...the emphatic rule that patients should be experimented upon, if at all, only with reference to their disease. Never should there be added to the gratuitousness of the experiment as such the gratuitousness of service to an unrelated cause."

Katz (4, at p. 727) has observed: "While a volunteering subject can be alert to protect his own self-interest, a patient-subject's need for treatment may cause him to overrate the benefits and underestimate the risks of a research technique." This statement was made in the context of having defined the volunteering subject as one who has not assumed the "sick role" while the patient-subject is one who has. May we assume that the volunteering subject is more autonomous than the patient-subject? Perhaps not. Lasagna and von Felsinger (4, at p. 623) conducted psychological tests on 56 "healthy young male volunteers", all of whom had participated in one or more clinical drug trials. These young men had been drawn from a college student population. In this group they found that 25 individuals had manifestations

of serious psychological maladjustment including three psychotics, twelve psychoneurotics, and so on. They further attempted to examine what factors motivated these "normal young men" to participate in the research. Many of the motivations might be viewed by detached observers as "illegitimate": eg, a search for "thrills" or "kicks"; escape or release from personal problems and drives; temporary relief from the boredom or pressure of everyday life; satisfaction of self-destructive urges; and so on.

Some sorts of individuals that might be assumed to have their autonomy limited have been identified earlier (2, at p. 51). In general, these are individuals who have been designated as having limited capacities to consent, having subordinate relationships to the investigator or his institution, or having--by virtue of other aspects of their life situations--especial vulnerability. One particular class of especially vulnerable individuals whose autonomy it will be most difficult to decide how to preserve is the dying person. How we might deal with especially vulnerable persons remains to be seen. To some extent, this depends upon whether the role of subject will be viewed as a right, a job, or a duty (2, at p. 56).

For the time being we must acknowledge the impossibility of determining with absolute assurance the prospective subject's freedom to make choices. The sensitive investigator will--to the extent possible--attempt to determine limits to autonomy through interactions with the prospective subject.

In the section on informing, the issues discussed as elements of information numbered 1, 3, and particularly 9 and 10 are designed to assist the individual who is negotiating with the prospective subject to make decisions

regarding the subject's autonomy (cf, Third Party Scrutiny).

Consent

Ordinarily, after the processes of informing, assurance of comprehension, and assurance of autonomy have been completed to a mutually satisfactory extent, the prospective subject signifies his willingness to become a subject by consenting. This process most commonly involves the signing of a consent form; however, in some cases written documentation of consent may be found unnecessary or undesirable (infra). Thus, it may be said that at this point a sort of contract has been established. Yet, as noted earlier, this type of contract is different in several important respects from the common commercial contract. Some of the differences have been mentioned earlier. Now another important difference emerges.

The process of consent can not be viewed as merely the consummation of a contract. The subject has already been informed (element of information number 10) that he is free to withdraw from the research at any time and that such withdrawal will in no way adversely prejudice his future interactions...and so on. In the context of medical practice it is clearly established that a patient may revoke or withdraw consent before or (if possible) during the medical procedure to which he has consented (7, at p. 261). This principle should certainly be at least equally applied to research. Thus, even after consent has been given, it is necessary to remain continually aware of the subject's continuing willingness to continue. In research activities requiring a high degree of commitment of the investigator's time or resources to a particular subject, as the research progresses, there is a progressively increasing motivation to the researcher to persuade a

subject to continue. The investigator must be aware of his own motivations and take care not to subjugate the will of the subject of his own (cf, Consent Committees and Third Part Scrutiny).

Standards for informed consent to research and practice

There seems to be nearly universal agreement that negotiations for informed consent to the investigator-subject relationship should meet higher standards than those for the physician-patient (or any analogous professional-client) relationship. This expectation for higher standards is reflected in most ethical codes and in the views of most commentators on the subject. However, there have been some recent departures from this viewpoint. Thus, for example, Capron (4, at p. 574) has asserted: "...the standard approach has it backwards. Higher requirements for informed consent should be imposed in therapy than in investigation, particularly when an element of honest experimentation is joined with therapy." Capron further points out that "...patients who are offered new therapy often have eyes only for its novelty and not for its risks."

In a subsequent publication (3) in the specific context of discussing consent to interventions for catastrophic diseases, Katz and Capron suggest that it makes little difference whether the intervention is formally classified as research or practice; the same sorts of information and other aspects of the negotiation will be determined by the characteristics of the proposed intervention.

Feinstein (22) has observed that there is indeed a "double standard" for informed consent in routine clinical practice and in clinical drug trials

(innovative therapy). He points out that: "An act that receives no special concern when performed as part of clinical practice may become a major ethical or legal issue if done as part of a formally designed investigation." He expresses the view that demands for formality in the consent negotiations should be determined by the "architecture of the clinical research". Thus, he distinguishes two types: 1) "Explicatory" the motive of which is to explain the mechanisms by which nature works, and 2) "Interventional" the motive of which is to change what nature has done or to thwart what it might do.

He argues that: "The demand for a totally informed consent seems reasonable whenever someone becomes a subject in an explicatory experiment. Since the imposed maneuver is personally unsolicited, medically unnecessary, and clinically non-beneficial, the potential subject should receive a complete disclosure of what is planned and what might happen."

However: "For each patient who enters a controlled clinical trial... the imposition of an experimental maneuver is personally solicited, medically necessary, and intended to provide clinical benefit. The investigator is acting as a doctor practicing medicine; and he engages in a doctor-patient relationship with each "subject". The only difference between the trial and other acts of clinical therapy is that the investigator, uncertain about which treatment is best to use, has decided to make the therapeutic decision for each patient in a pre-planned (usually randomized) rather than ad hoc judgmental manner."

Thus, he proposes, that the negotiations for informed consent in interventional clinical research (innovative therapy) may be allowed to conform more to the norms of medical practice than to those of explicatory research. Parenthetically, there are presented here only the major points providing the rationale for Feinstein's position; a more fully developed argument may be found in his article.

In this paper, the author takes the position that patients (or other clients of professionals) are entitled to the same degree of thoroughness

of negotiations for informed consent as are subjects. However, for reasons stated earlier (1, at p. 3) the patient (client) should, in general, be allowed more freedom than the subject to relinquish this entitlement. In other words, patients may be offered the opportunity to delegate decision making authority to a physician while subjects (of any experiment bearing any consequential possibility of harm) should rarely be offered this option. The most important distinction between the negotiations for informed consent in the two contexts (research and innovative therapy as opposed to practice) is that the prospective subject must be informed that if the proposed activity is research or innovative practice, the subject will be at least in part a means and perhaps only a means to another end (1, at p. 3).

In general the negotiations for informed consent to innovative practice will be more complex than those to pure research where there is no intent to bring direct health related benefit to the subject. The greatest problems will be making clear to the prospective subject the extent to which he, as opposed to others, might be expected to reap the benefits of the proposed activity.

It is commonly asserted that, while there are many cases in which physicians have been found negligent for having failed to provide full disclosure in the context of medical practice, there is but one case in which an investigator was found negligent on the same grounds: Halushka v. University of Saskatchewan (4, at p. 569). Yet, examination of several medical

malpractice cases found against physicians for failure to provide full disclosure reveals that what was not fully disclosed is that the procedure used was experimental, novel, or innovative; eg, Slater v. Baker and Stapleton (4, at p. 526), Natanson v. Kline (4, at p. 529), Fiorentine v. Wenger (4, at p. 529).

Supervision of the negotiations

Consent committees

It has been suggested by several individuals that--at least in some sorts of research--each of the four component processes of informed consent might be more effectively accomplished if the entire process were to be observed--and, perhaps, participated in--by some third party. This third party might be either an individual or a group charged with the responsibility to see that the best interests of prospective subjects were served. The first formal proposal to establish such a group may be found in the DHEW draft proposal (13) for protection of those human subjects defined as having "limited capacities to consent"; eg, children, the abortus, the fetus in utero, products of in vitro fertilization, prisoners, and the institutionalized mentally infirm. In the introduction to this draft it is stated that:

"Protection Committees are to be established...to provide "supplementary judgment" concerning the reasonableness and validity of the consent given by, or on behalf of, subjects. The intent of this policy is that institutions which apply for DHEW funds or submit research in fulfillment of DHEW regulations, must be in compliance with these special protections, whether or not particular research, development, or demonstration activities are Federally activities (sic)."

A definition of "supplementary judgment" is provided in the same draft. A detailed description of the composition and duties of the protection committee for each category of research is further provided.

In a subsequent draft (14) of proposed policy DHEW "...proposes an extensive revision in this innovative concept. Initially, it acknowledges that the term "protection committee" is pejorative and proposes the term "consent committee" as more appropriate and consistent with the primary purpose of such bodies. Further, it proposes to eliminate specific requirements for the size and composition of such committees".

The introduction proceeds to point out that much of what had been specified earlier will be made a matter of local (applicant institution) option subject to approval at the departmental level by the Ethical Advisory Board. Consent committees continue to be proposed for all categories of research described in this proposed policy (all categories mentioned for the earlier draft with the exception that the revised proposal for children was "reserved" for subsequent publication).

The proposed duties of the consent committee include the following:

"...to oversee the actual process by which individual subjects are selected and consents...are secured, to monitor the progress of the activity (including visits to the activity site on a regular basis) and the continued willingness of the subjects to participate, to intervene on behalf of one or more subjects if conditions warrant, and to carry out such other duties as the Secretary may prescribe."

Further, other duties of the consent committee may include:

"(1) Participation in the actual process by which individual subjects are selected and their consents secured to assure that all elements of legally effective informed consent...are satisfied...this might require approval by the committee of each individual's participation as a subject in the activity or it might simply call for verification (e.g., through sampling) that procedures prescribed in the approved application or offer are being followed."

"(2) Monitoring the progress of the activity and the continued willingness of subjects to participate." This might include: "...identification of one or more committee members who would be available for consultation with subjects at the subjects' request, continuing evaluation to determine if any unanticipated risks have arisen and that any such risks are communicated to the subjects, periodic contact with the subjects to ascertain whether they remain willing to continue..., providing for the withdrawal of any subjects who wish to do so, and the authority to terminate participation of one or more subjects with or without their consent where conditions warrant."

(b) The size and composition of the consent committee must take into account such factors as:

"(3) Whether the membership has been so selected as to be competent to deal with the medical, legal, social, and ethical issues involved in the activity; (4) whether the committee includes sufficient members who are unaffiliated with the applicant or offeror apart from membership on the committee; and (5) whether the committee includes sufficient members who are not engaged in research, development, or related activities involving human subjects. The committee shall establish rules of procedure for carrying out its functions and shall conduct its business at convened meetings, with one of its members designated as chairperson."

There is a provision under which an applicant or offeror may request of the Secretary a modification or waiver of the requirement for a consent committee where a particular activity involves negligible risk to the subjects.

It is quite clear that the intent of the proposal to develop consent committees was to enhance the likelihood of success of each of the four components of negotiating informed consent. While there is little cause to question that the existence of consent committees would contribute to this goal, there is no cause to suspect that their existence would result in perfection of the negotiations for informed consent. In a position paper submitted by the Association of American Medical Colleges in testimony to the Commission (24) it is argued that the costs (time, money, and,

perhaps most importantly, social costs) of developing consent committees as described in DHEW proposals might far outweigh the expected benefits to the process of negotiating informed consent. It is further proposed that similar improvements might be achieved through far less costly means. In particular, it is proposed that--at the discretion of the investigator (whose discretion will be reviewed and perhaps modified by the IRB)--"third party scrutiny" of the consent process might be offered as an option to some subjects; in some other cases a requirement for third party scrutiny might be imposed whether or not the subject (or, for that matter, the investigator) wishes it.

While the final DHEW regulations governing research on the fetus (15) make no mention of consent committees, the possibility that they might be required for other categories of prospective subjects having limited capacities to consent still exists. Therefore, the concept of the consent committee merits serious consideration by the Commission.

In the opinion of the author, the entire research process and all of its participants stand to lose more than they might expect to gain from the establishment of formal consent committees as described in DHEW proposed policies. The reasons for this position are essentially those detailed in the above cited position statement (24). In its place, one might consider extending the use of third party scrutinizers.

Third party scrutiny

The necessity for offering the third party scrutinizer, either as an option or as a requirement, should be the responsibility of the IRB. The

third party scrutinizer may be assigned any of the responsibilities specified for the consent committee in the DHEW proposal.

The types of individuals that might be employed as third party scrutinizers were identified earlier (Informing, element no. 9). This individual should be someone whom the prospective subject will recognize as a trusted advisor. Most commonly, this will be a "physician-friend"; in other cases depending upon the nature of the decision-making problem and the wishes to the subject it might be a clergyman, a lawyer, a relative, or some other appropriate professional or nonprofessional advisor.

The types of research for which third party scrutiny might be found useful are those which have some or all of the following features. The subject may be called upon to assume substantial risk or inconvenience particularly when there is no expectation of direct health related benefit. In a proposal to conduct a therapeutic innovation, there may be legitimate competing alternatives; this presents a particular problem when the choice of one might foreclose any possibility of reverting to the alternative if the one chosen should fail. (Informing, element no. 7). There may be some cause to suspect substantial barriers to comprehension or autonomy (cf, Comprehension and Autonomy).

In such cases during the negotiations for informed consent it may be proposed to the prospective subject that he might wish to enlist the services of a third party scrutinizer. He might further be alerted as to the general types of functions there might be for such a person in this particular research proposal. He might further be advised as to what sorts of persons

he might wish to choose to assume this role. After receiving all of this information, ordinarily the prospective subject should have the option to refuse the services of a third party scrutinizer. Imposition on the subject of a requirement for a third party scrutinizer is a serious step. It is a potential invasion of privacy (particularly when the scrutinizer is to be chosen by the institution, and even more particularly, when the individual is not an agent or employee of the institution conducting the research (24). Also, imposing such a requirement will, at times, be tantamount to a declaration to the prospective subject that his judgment (ability to comprehend; ability or freedom to make choices; and so on) is to be questioned. However, in some cases this will be necessary.

Illustrative example: There follows an example of how and why an IRB imposed a requirement for third party scrutiny of a portion of the process of negotiating informed consent in a particular research protocol. This example is selected for several reasons. The proposed subject population was at least potentially vulnerable by virtue of two attributes not identified in existing or proposed DHEW regulations or policies. Further, the analysis of risks and of hoped for benefits were both complex.

The research maneuver involved inserting a catheter into the coronary sinuses for purposes of sampling blood to assay a substance made in the heart. Under no circumstances was the catheter to remain in the coronary sinus longer than 10 minutes. The subject population was individuals who had been admitted to a coronary care unit very recently with known or suspected myocardial infarctions. No subject would be enlisted who did not require catheterization of the right side of the heart for "practice" purposes. No "extraordinary" measures would be taken to place the catheter

in the coronary sinus in individuals in whom such placement was found to be difficult.

In other words, all possible measures were taken to minimize the probability of harm. Yet there remained a very small probability of harm in the form of arrhythmia. The facilities available for monitoring for the occurrence of this harm were optimal; the probability of success of interventions proposed to counteract a arrhythmias had a very high likelihood of success.

No direct benefits to the subjects were anticipated. The subjects would receive the benefit of the catheterization indicated for practice purposes. As discussed earlier (2, at p. 35) because the period of very close monitoring would be extended, there was an enhanced likelihood of detecting various complications (of the myocardial infarction) promptly and, when possible, initiating definitive treatment. There was a moderately large probability of a very large benefit to the population of individuals having myocardial infarctions. The investigators were attempting to identify a chemical which might contribute to the morbidity and mortality of this disease; if they were able to establish the relationship it would be possible to intervene directly; means for blocking the formation as well as the effects of this chemical already exist. Prior studies done in animals and in humans not having myocardial infarctions indicated a reasonably high probability of associating this chemical with the pathogenesis of the disease.

In medical practice it is customary to assume that any stress may be harmful to individuals with myocardial infarctions. Thus, great care is taken to avoid physical and psychological stresses particularly during the

early stages of treatment. Parenthetically, it is not proved that psychological stress increases the morbidity or mortality in this disease. Patients with known or suspected myocardial infarctions are commonly treated with narcotics to diminish pain and anxiety. Thus, most individuals whom the investigators might approach to negotiate informed consent for this research will have recently received treatment with a narcotic.

In the judgment of the IRB, the negotiations for informed consent would create anxiety. This, in turn, might jeopardize the physical and psychological well-being of the prospective subject. (As noted earlier, this could not be proved.) Further, it was judged that the proposed research population was especially vulnerable for either of two reasons:

- 1) Some of these individuals might perceive themselves as in the process of dying; in some cases this perception might be in accord with facts.
- 2) Some of these people might have had their abilities to make rational judgments impaired by virtue of having received a narcotic; ie, a state of inebriation would have been induced.

Thus, the IRB imposed a requirement for partial scrutiny of the consent process by two different types of third parties:

- 1) Before any approach to the prospective subject was made, the investigator would review the proposal--all elements of information--with the next of kin. The purpose of this discussion was to determine if--in the view of the next of kin--this is the sort of thing to which the prospective subject might be expected to consent. If in the judgment of the next of kin, the answer was no, no approach to the prospective subject would be made.

2) A physician not connected with the research and who, by virtue of his relationship to the prospective subject, had the best interests of the prospective subject in mind would be called upon to determine that:

a) The patient's physical and psychological condition were such that he was not likely to be unduly threatened or harmed by the consent negotiations, and

b) the patient's cognitive function had not been impaired to the extent that he could not understand the information.

The physician assigned responsibility to make these determinations was to be the one who had most recently examined the patient sufficiently thoroughly to make these determinations. When possible this would be the patient's personal physician who had established a physician-patient relationship prior to the onset of the current illness. When no such relationship existed or when the physician meeting this description was unavailable, the physician called upon for this judgment would be the resident physician in the coronary care unit. In the event the personal physician was also a member of the research team, he would be disqualified as a third party scrutinizer.

In this case, the investigators were cardiologists who are highly skilled and experienced not only in catheterizations of the heart but also in the management of patients with myocardial infarction in the coronary care unit. Thus, it was judged unnecessary to have any other physicians in attendance during the process of negotiating for informed

consent or during the brief period during which the research maneuver was performed. In the event the subject wanted to see his own physician during this period his access to that physician would be no more limited than it would ordinarily be in the usual conduct of activities on a coronary care unit. The circumstances of the research were such that it would not be in the scientific interests of the investigators to continue the research if something "went wrong".

Other examples of research in which a requirement for third party scrutiny of all or part of the negotiations for informed consent can be provided should the Commission wish them. It is the view of the author that regulations for third party scrutiny of negotiations for informed consent should impose on the IRB the requirement for determining when it will be necessary and what form it should take. Regulations that attempt to prescribe the form and substance of third party scrutiny may deprive the IRB of the flexibility necessary to meet the needs of particular research proposals and particular prospective subjects.

Documentation of informed consent

DHEW regulations prescribe in section 46.10 the forms in which informed consent must be documented. Three possible forms are described (5):

"(a) Provision of a written consent document embodying all of the basic elements of informed consent. This may be read to the subject or to his legally authorized representative, but in any event he or his legally authorized representative must be given an adequate opportunity to read it. This document is to be signed by the subject or his legally authorized representative. Sample copies of the consent form as approved by the Board (IRB) are to be retained in its records.

"(b) Provision of a "short form" written consent document indicating that the basic elements of informed consent have been presented orally to the subject or his legally authorized representative. Written summaries of what is to be said to the patient are to be approved by the Board. The short form is to be signed by the subject or his legally authorized representative and by an auditor witness to the oral presentation and to the subject's signature. A copy of the approved summary, annotated to show any additions, is to be signed by the persons officially obtaining the consent and by the auditor witness. Sample copies of the consent form and of the summaries as approved by the Board are to be retained in its records."

The third "form" is, in fact, not a form; it reads in part as follows:

"(c) Modification of either of the primary procedures outlined in paragraphs (a) and (b) of this section. Granting of permission to use modified procedures imposes additional responsibility upon the Board and the institution to establish: (1) That the risk to any subject is minimal, (2) that the use of either of the primary procedures for obtaining informed consent would surely invalidate objectives of considerable immediate importance, and (3) that any reasonable alternative means for attaining these objectives would be less advantageous to the subjects."

The regulations go on to require that the reasons for permitting the use of modified procedures must be individually and specifically documented and made a matter of permanent record.

Careful reading of the quoted portion of paragraph (c) will indicate that--since all three criteria must be met--modified procedures may virtually never be used. If the word "and" preceding "(3)" were changed to "or", some flexibility might be permitted by this paragraph.

It is difficult to understand the implications of these regulations without an awareness of how they are implemented by DHEW officials having such authority. Thus, an illustrative example is provided:

Since these rules and regulations were promulgated it has been NIH policy to require informed consent documented as specified in either paragraph (a) or (b) to use tissues or fluids removed at either surgery or autopsy for research purposes (25). This requirement is imposed even

though the autopsy or surgical procedures are done in accord with customary medical practice, where there is no removal or retention of additional tissues or fluids for research purposes (beyond the amount required by the medical needs of the patient or next of kin), and where the procedures themselves are authorized by consent (of the sort usually used in the medical practice context) to remove, retain, and dispose of tissues. Further, this requirement is imposed even if there is no way to link the information that might be developed through the research to the name of the individual from whom the tissue or fluid was removed. Thus, it is asserted that current DHEW regulations--although they seem to permit reasonable flexibility--actually permit very little. The consequences of this sort of interpretation of the regulations will be analyzed subsequently (Conditions under which consent negotiations may be less elaborate).

The regulations of the Food and Drug Administration do permit some flexibility (26).

Section 310.102 (a) specifies that "...the use of investigational new drugs on humans shall impose the condition that investigators "obtain the consent of such human beings or their representatives, except where they deem it not feasible or, in their professional judgment, contrary to the best interests of such human beings."

"(b) This means that the consent of such humans (or the consent of their representatives) to whom investigational drugs are administered primarily for the accumulation of scientific knowledge, for such purposes as studying drug behavior, body processes, or the course of a disease, must be obtained in all cases, and, in all but exceptional cases, the consent of patients under treatment with investigational drugs or the consent of their representatives must be obtained."

(d) Defines exceptional cases as "...those relatively rare cases in which it is not feasible to obtain the patient's consent or the consent of his representative, or in which as a matter of professional judgment exercised in the best interest of a particular patient under the investigator's care, it would be contrary to that patient's welfare to obtain his consent."

"(g) "Contrary to the best interests of such human beings" applies when the communication of information to obtain consent would seriously affect the patient's well-being and the physician has exercised a professional judgment that under the particular circumstances of this patient's case, the patient's best interests would suffer if consent were sought."

This section goes on to specify that consent to receive an investigational new drug in Phase I and Phase II shall be in writing. When consent is necessary under such rules in Phase III investigations, it is the responsibility of investigators, taking into consideration the physical and mental state of the patient, to decide when it is necessary or preferable to obtain consent in other than written form. When such written consent is not obtained, the investigator must obtain oral consent and record that fact in the medical record of the person receiving the drug.

These quotes from FDA regulations indicate that this agency is willing to permit more flexibility than is DHEW not only in the documentation of but also in the nature of the negotiations for informed consent. These regulations might be criticized on grounds that they leave too much to the judgment of the physician (investigator). However, section 312.1 imposes the necessity for an "institutional review committee" (analogous to the IRB) which is assigned responsibility for, among other things, imposing group judgment on the plans for negotiations for and documentation of informed consent.

The provision in FDA regulations that in exceptional cases, it might be appropriate to conduct phase III drug trials according to reduced standards of consent recognizes that in some situations according to the judgment of the physician-investigator, negotiating informed consent might be contrary to the welfare of a particular patient. In general, this provision is meant to recognize two sorts of contingencies. The first is the

situation in which a Phase III drug must be administered immediately in order to have optimal effect. If time is taken to negotiate informed consent, the patient-subject might sustain irreversible injury as a consequence of the delay. It is not extraordinary that physician-investigators ^{and receive from} ask of the IRB permission to proceed with sufficient flexibility [^] to accommodate the demands of an emergency situation.

The second is the situation in which the patient-subject might for various reasons not wish to know some of the facts enumerated as elements of information. Most commonly, this calls to mind the patient with some dread disease who might be harmed psychologically by inappropriately premature full disclosure of the diagnosis. However, there might be many other points of material information with which the patient-subject might not wish to be bothered. As Louisell and Williams have observed in the context of medical practice (27, at.p. 594.63): "...Some patients do prefer not to know the details, including the risks, of proposed procedures. Their attitude frankly is: "Doctor, I engaged you because of my confidence in your judgment and skill. I cannot understand all the implications of what you propose to do, and I do not wish to try. Because of my confidence in you, and my own ignorance and fears, I ask you to bear on your shoulders not only the medical burden of the procedure, but the moral one of the decision." If that is the true attitude of the patient, and he clearly conveys it, there is no reason in law, morals, or public policy why the physician normally should not abide it, if he is willing to do so."

Thus, in the context of medical practice, it seems to be the right of the patient to waive any element of informed consent he wishes. However,

as discussed elsewhere, the subject ordinarily should be much more cautious about delegating decision-making responsibility to the investigator. The author can recall no proposal by an investigator to the IRB at Yale University School of Medicine to withhold information from a prospective subject because--in the judgment of his physician--full disclosure (particularly of the diagnosis) would be contrary to his best interest (except, as noted earlier, in cases of emergency).

The consent form

In almost every research activity involving consequential risk or inconvenience to the subject it is most appropriate to document in writing the fact that appropriate negotiations for informed consent have been conducted. Exceptions will be specified in subsequent sections.

In the experience of the author, the consent form used by virtually every investigator is of the sort specified in section 46.10 (a) of the DHEW rules and regulations. The view prevails among investigators that the "short form" prescribed in 46.10 (b) offers no advantage to either investigator or subject. If the same quality and quantity of information is to be presented to the subject in form (b) as in form (a), and if all this information is to be committed to paper no matter which form is used, there seems no advantage to not giving the subject a copy of that paper to read, sign and--as discussed subsequently--keep. The author recalls no case in which an investigator proposed to the Yale Medical School IRB to use a "short form" as described in the regulations. Through the Commission's IRB study it will be seen if this experience is shared by

most or all other IRBs.

In general, it should be kept in mind by all concerned--but particularly the investigator and members of the IRB--that the consent form can almost never be so constructed as to anticipate all of any particular prospective subject's wishes to be informed. The consent form is most effective when it is viewed by the investigator as an instrument designed to guide him in his negotiations with the prospective subject. The consent form should contain at least the minimum amount of information and advice that should be presented during the negotiations for informed consent. If any substantive new understandings are developed in the process of the negotiations which have any bearing on the prospective subject's willingness to participate these should be added to the consent form signed by that particular individual.

The consent form should present an adequate coverage of each of the eleven elements of information (section on Informing) that are germane to the particular proposed research activity. The fact that the consent form is considered a guide to the negotiations should be specifically reflected as indicated in element number 8 calling for an offer to answer any inquiries concerning the procedures. It should be made clear that this offer to respond to inquiries is, in fact, an offer to elaborate on any of the eleven elements of information to the extent that the prospective subject wishes.

The use of general consent forms designed to document consent for research generally or even for several categorically related research protocols should be discouraged. At the very least, a consent form should

be designed to meet the specifications of a particular research proposal. A fully satisfactory document designed to meet the needs of one particular protocol may, as discussed above, undergo further modification to reflect alterations in the negotiations that occur as a consequence of discussing the proposed research with individual subjects. At times it is necessary to design more than one consent form for use in a single research protocol. Thus, for example, when a protocol is designed to conduct the same maneuvers on two distinctly different populations of subjects--eg, diabetics and healthy volunteers--it is ordinarily appropriate to have separate consent forms for each class of subject. Many of the elements of information presented to the diabetics will differ from those presented to the healthy volunteers. Thus, for example, element number 3 would contain very different information as to why the prospective subject has been selected. It might also contain very different sorts of information regarding "pretests" to determine eligibility and the consequences of "failure to pass" these examinations. Further, the nature of the benefits to be derived is likely to be very different.

Many institutions have guidelines prescribing the type of language that ought to be used in the consent form. Most commonly it is suggested that the form be worded in language that the "average lay person" should be expected to understand. This suggestion has provoked considerable controversy. For example, what is an average lay person? And what can he be expected to understand? Many protocols are designed to involve subjects that depart in some substantial way from "average". For example, some studies are designed to involve subjects who have serious chronic diseases in whom "standard and accepted" therapeutic measures have failed.

Commonly, such individuals have a highly sophisticated understanding of the technical language used to describe their disease, various means of diagnosis and therapy, and the harms that may occur as a consequence of therapy or of not being treated. On the other hand, some protocols are designed to involve naive subjects who might have little schooling, who might have primary languages other than English, and so on. Thus, it seems more appropriate to suggest in guidelines that the consent form should be presented in language that the prospective subject might be expected to understand. Protocols in which it is planned to draw upon diverse populations for subjects might require more than one consent form.

Various institutions have developed further recommendations on the language of the consent form. Some institutions have policies requiring that the entire consent form be worded in the first person. Thus, the various elements of information each begin: "I understand that the purpose of the study is to..."or "I hereby agree to have Dr. Jones draw 10 cc (2 teaspoons) of blood...". Other institutions recommend that consent forms be worded in the second person. For example: "You are invited to participate in a research project designed to...(accomplish some purpose)." "If you agree to participate there is a small possibility that you might develop a rash." "The purpose of this research is not to bring direct benefit to you but rather to develop information which might help us design better diagnostic methods for persons like you in the future."

The preference of the author is for consent forms that present the elements of information in the second person. After the elements of in-

formation have been presented there may be a statement worded in the first person entitled "Authorization: I have read the above and decide that...(name of subject) will participate in the project as described above. Its general purposes, the particulars of involvement, and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form."

In the view of the author, the presentation of the information in the second person followed by an authorization written in the first person best conveys the sense of negotiation (of give and take) involved. However, the author is not aware of any documentation that one style of language is to be preferred to another.

At the conclusion of the consent form there should be a line provided for the signature of the consentor. There should further be some means of specifying how the consentor is related to the subject (self, parent, guardian, and so on). It should also specify the date on which the form was signed. Some individuals may wish to also record the date on which the form was first presented to the prospective subject if it differs from that on which it was signed. In cases where proxy consent is obtained a space may be provided for the signature of the actual subject if appropriate. This signature may indicate, depending upon the situation, the actual subject's consent (which may or may not be legally valid), his assent, or, perhaps, merely his awareness that somebody is consenting to something on his behalf.

Also on the consent form there should be a space provided for the signature of the individual who has conducted negotiations for consent. His telephone number should be provided in the event the prospective subject

(or subject) has any wish to discuss the project further. In cases where a third party scrutinizer has participated in the consent process, a space should be provided for his signature as well. In addition, it might be of value in some consent negotiations to provide the names and telephone numbers of other individuals who might be consulted by the prospective subject or his agents for further information. The most common situation in which it is advantageous to list the name(s) and telephone number(s) of other individuals is when consent for a complex research activity is obtained by someone other than the professional who is responsible for the conduct of the activity (cf, Who should negotiate for informed consent?)

Prohibition of exculpatory clauses

DHEW regulations (5) require under section 46.9 that: "No...informed consent, oral or written,...shall include any exculpatory language through which the subject is made to waive, or appear to waive, any of his legal rights, including any release of the institution or its agents from liability for negligence." The author finds no cause to elaborate, modify, or challenge this requirement as being applicable to all negotiations for informed consent.

Who keeps records of informed consent?

There seems to be general agreement that the IRB should keep copies of the general consent forms offered to each prospective subject of any particular activity. A copy of the consent form (or the various consent forms) used to document the negotiations for informed consent is made part of the permanent record of each protocol that is retained by the IRB. There have been various proposals that the IRB should also keep copies of the consent forms signed by each subject. The author suggests that this

would in some cases be detrimental to the best interests of the subjects; the reasons for this suggestion are the same as those presented for avoiding having the signed consent forms made a part of the permanent records of the institution (infra).

The investigator should ordinarily assume the responsibility to retain the consent forms signed by the individual subjects. It should be his responsibility to safeguard the confidentiality of these forms when appropriate and to the extent necessary. To some extent the mere fact that an individual has agreed to serve as a subject of a particular research activity will reveal information about that subject that he might not wish to have generally known. Thus, for example, the consent form might specify: "You are invited to participate in this research project because you have cirrhosis of the liver." Various rules and regulations specify how long the investigator ought to retain these consent forms in his files. Since one of the purposes of documentation of informed consent is to protect the investigator from inappropriate litigation for failure to provide "full disclosure" it is recommended that the signed consent form be held for a period of time slightly greater than the statute of limitations for such actions in his jurisdiction. Ordinarily, signed forms should be retained for a sufficient period of time longer than the statute of limitations as usually advised for physicians who are concerned with potential malpractice litigations; this is usually about six months but, in states having "discovery statutes", it may be forever (7, at p. 322).

Many institutions have policies that signed consent forms should be made part of the permanent records of the institution. This is based upon three assumptions: 1) If there is any litigation against the investigator, the institution is likely to be named as a co-defendant. 2) Institutional administrators commonly believe that the record keeping systems of the institution are superior--in various ways--to those of investigators. 3) Investigators may move away from the institution to take employment elsewhere. In such cases, the signed consent forms might not be available to the institution when they are needed. Each of these assumptions is at least in part true. The only one that might be seriously challenged by some investigators is the second. Some investigators are more adept at keeping orderly records than almost any institution. The relatively smaller number of records they keep as well as the relatively smaller number of individuals who have access to these records each contribute to their lesser likelihood of losing a record.

On the other hand, individual investigators or small groups of investigators are much more likely to be able to provide assurance of confidentiality than are large institutions. In general, when confidentiality is a significant issue, the author recommends that the investigator be assigned primary responsibility for keeping signed consent forms.

In most cases the subject should be given a copy of the consent form bearing all the signatures that are to be placed on that form. Since, as discussed earlier, this is a form of contract, it seems only appropriate to give the subject a copy. Also, providing the subject with

a copy of the form will afford him an opportunity to continue to get more information as additional questions occur to him. It will also be available as a constant reminder of his freedom to ask questions, to withdraw without prejudice, and so on. Finally, as suggested above (cf, Consent form) the form may provide the name(s) and telephone number(s) of individuals he might wish to contact as necessary.

Who should negotiate with the prospective subject?

Some institutions have policies prescribing more or less specifically who may negotiate with the prospective subject for informed consent. Thus, for example, some hospitals require that if the principal investigator on a research activity is a physician, the responsibility for negotiating for informed consent cannot be delegated to a non-physician. Some students of or commentators on the informed consent process have suggested that the quality of informed consent might somehow be reduced by virtue of the fact that a physician-investigator delegated responsibility for informed consent negotiations to a research-nurse or, perhaps, even to a non-professional (28, at pp. 212 et seq). The question thus arises as to whether there is any need for regulations defining who may participate in the consent negotiations either generally or in relation to particular classes of research. After weighing the pros and cons of having various types of individuals negotiating for informed consent, the author will conclude that a good general guideline might be developed as an analogy to the laws governing the authority of the physician to delegate responsibilities to various individuals based upon

his judgment that they are sufficiently trained or experienced to perform the responsibility adequately and that the physician is held accountable for the actions of those to whom he delegates responsibility. In general, these statutes are written to control medical practice and, further, are written to permit delegation of authority to various types of "physicians trained assistants". However, it is now proposed that this model might be applied to the negotiations for informed consent in a research context and, further, that the type of professional might be extended to include all sorts of qualified investigators in addition to physicians.

In general, as one examines the various component processes of the negotiations for informed consent, it might be assumed that various types of professionals might be better equipped to accomplish each of these purposes--either by virtue of their training or expertise or by virtue of their motivations--than others. The principal investigator will ordinarily be better informed about the technical aspects of the research than will other members of the research team. Thus, if he is willing, he will be more capable of responding to detailed questions about risks, benefits, alternatives, and so on than will most others. Professionals who are equally certified might be expected to have approximately the same amount of detailed information at their disposal.

On the other hand, in the context of medical practice, particularly in large institutional settings, it has been observed that patients tend to be better informed when a professional who is not a physician is assigned responsibility for their "education". It seems that such professionals as clinical pharmacists, physician's assistants, nurse practitioners, and so

on, are generally more oriented toward patient education than are most physicians. There are, of course, clear individual exceptions to this generalization. However, there is no a priori reason to assume that subjects will in general be better informed merely because it is the principal investigator who undertakes the responsibility for informing them.

Much has been written about barriers to comprehension that are created when the individual negotiating with the prospective subject is of a very much different social class or has a very much higher degree of education than the prospective subject. Perhaps, it might be reasonable to suppose that the more equal the negotiators are in these two categories the more likely there is to be comprehension. In addition, relative equals would probably be more capable in perceiving non-verbal manifestations of non-comprehension.

As discussed earlier (cf, Autonomy), when the prospective subject has assumed the "sick role" there immediately exists a barrier to his autonomy. In this paper it is intended to expand the definition of "sick role" beyond the confines of what is ordinarily termed a patient. The very same sorts of problems exist when a person assumes analogous roles in educational or social contexts. In these contexts, because of the social demand upon the "sick individual" to get well, he may find it difficult to refuse to "cooperate" with a professional whom he believes has the power to "make him well".

It is concluded, that there is no a priori reason to predict that individuals other than the principal investigator will be more or less successful in negotiating (as contrasted with securing or obtaining) informed consent. It is suggested that the individual(s) assigned this responsibility

within a research team be the one(s) who seems most capable and most interested in performing this role. In the event this is a person having professional qualifications or certification lower than that of the principal investigator this should be made clear during the consent negotiations. In such cases it is ordinarily advisable to name the principal investigator (or one of his equally certified co-investigators) on the consent form and to provide instructions as to how he might be made available to respond to questions that--in the view of the prospective consentor--cannot be answered adequately by the individual with whom he is negotiating. The principal investigator should be held accountable for the actions of all individuals to whom he delegates responsibility. The selection of the individual(s) who will function as negotiators for informed consent in any particular research project should be determined by the principal investigator. The IRB should review this designation and make recommendations or impose requirements for modification as appropriate.

Access to prospective subjects

In some research proposals a prospective subject population will be identified as one to which the investigator would not have access in the course of his customary professional activities. Thus, the investigator may wish to secure the names of prospective subjects through contact with practicing professionals (eg, physicians, social workers, and so on) or through the records of physicians, hospitals, schools, welfare agencies,

and so on. In many cases the clients of these professionals or institutions may assume that their relations with the professionals or institution are, at least in part, confidential. Thus, when this mode of access to a prospective research subject is to be used, it ordinarily becomes necessary to involve the practicing professional or his institutional record system in the consent process in a way that minimizes the potential for violations of confidentiality or coercion.

One mechanism that is commonly used is to have the investigator initiate contact with the practicing professional. The investigator may provide the practicing professional with a form letter which might be addressed to suitable prospective subjects. This letter might describe in general terms the proposed research activity and suggest to the prospective subject that should he have any interest in participation, he might initiate direct contact with the investigator. At that point negotiations for informed consent might commence as in any other research context. When appropriate, the prospective subject should be advised in the communication from the practicing professional that not only is there no need to inform the practicing professional whether the client consents to become a subject, but also (when appropriate) the investigator will not reveal to the practicing professional whether an investigator-subject relationship has been established. Thus, to the extent necessary, it is possible to minimize potentials for violations of confidentiality as well as potentials for coercion or duress. The latter potential presents itself most significantly in research designed to develop new knowledge on some characteristic of the professional-client interaction.

In some other situations the prospective subject may be the client of a professional whose overall "care" of the client is dependent upon his awareness of all activities that might have any influence on the "health" of the client. In such circumstances, no matter how access to the prospective subject is established, negotiations for informed consent should not proceed until the consent or approval of the practicing professional has been obtained. In such cases, full disclosure would demand that the prospective subject be informed that the research is proceeding with the awareness of the practicing professional who will be kept informed of any consequential findings, adverse reactions, and so on. In general, in most hospitals, there exist policies requiring that the personal physician of the patient be asked to approve the involvement of the patient in a research activity.

As discussed above (section on Third Party Scrutiny) the practicing physician may be called upon to serve the role of third party scrutinizer.

Timing of the negotiations for informed consent

To the extent possible and necessary adequate time should be provided to accomplish the objectives specified under elements of information numbered 4e, 8, 9, and in the sections entitled Comprehension, Autonomy, and Third Party Scrutiny.

In addition, in many types of research proposals it is planned to do the research on individuals who will be relatively incapacitated, distracted, or preoccupied at the time the research will be done. Thus, for example, if it is planned to investigate an innovative approach to delivering a baby, it is possible to identify a suitable population of

prospective subjects weeks or months before the research will be done on any particular subject. Ordinarily, it would be preferred to negotiate informed consent during or after a routine pre-natal visit with the obstetrician rather than when the woman is experiencing the discomfort and anxiety of labor and, perhaps, has been already treated with drugs that might influence her cognitive function. In general, the obstetrician's office is an environment more conducive to rational decision making than is the labor or delivery room (28). Also, prospective subjects contacted during a routine pre-natal visit will have the time to accomplish the various functions specified in the preceding paragraph.

In situations in which informed consent has been negotiated well in advance of the proposed research, the prospective subject should be reminded of his right to withdraw without prejudice shortly before the research maneuver is initiated.

In some other circumstances, it will be impossible to conduct the consent negotiations at a time and in an environment that is most conducive to high quality decision making; see for example, the illustrative example provided in the section on Third Party Scrutiny.

Conditions under which consent negotiations may be less elaborate

Thus far, this paper may have created the impression that the average negotiation for and documentation of informed consent must be an extremely elaborate process. This false impression derives from the fact that an attempt has been made to present a comprehensive account of the

various factors that must be considered by and the various devices available to individual(s) who are planning negotiations for informed consent. In fact, in most cases most of these factors and devices will be found inappropriate or unnecessary. Each negotiation for informed consent must be adjusted to meet the requirements of the specific proposed activity and, more particularly, be sufficiently flexible to meet the needs of the individual prospective subject. By way of illustration, most consent forms approved by the IRB at Yale University School of Medicine contain less than one half page of single-spaced text. Sample consent forms published by the UCSF Committee on Human Research (29) contain approximately the same amount of information.

Ingelfinger in an article entitled "The Unethical in Medical Ethics" has expressed alarm over the increasing apparent need for review of research by various types of committees; excessive formality and documentation of informed consent, and so on (30). Among other things he predicts that continuation of current trends will have egregious consequences. He expresses his alarm with the:

"...dilution and deprecation of the important by a proliferation of the trivial. The patient, asked to sign countless releases or consents, may respond with a blanket refusal or with a proforma signature. The physician, immersed in a profusion of unimportant detail will lose sight of, and respect for the important issues. Perhaps he will feel compelled to practice defensive ethics--no more honorable than defensive medicine. For medical ethics, in short, trivialization is self-defeating".

Thus, he draws on the experience of observing the behavior of physicians in reaction to their awareness of ever increasing possibilities for malpractice litigation. Physicians now obtain many more diagnostic tests than are necessary. This custom is referred to as the practice of defensive medicine (7, at p. 414 et seq). It is enormously expensive for all concerned. The analogy to

which he attempts to call attention--defensive ethics--would include highly formal negotiations for informed consent to research procedures involving minimal involvement, risk, or discomfort to the subject.

Ingelfinger earlier expressed his view that--particularly in biomedical experimentation (including therapeutic innovation)--consent is generally informed only technically but virtually never educated (31). He argues powerfully that the individual who has assumed the sick role is virtually never capable of either adequate understanding or total freedom of choice. He sees the relationship that might be created by educated consent as described by Jonas (supra) (21) or Ramsey--a "...covenantal bond between consenting man and consenting man (that) makes them... joint adventurers in medical care and progress..." as essentially unattainable and utopian ideals. He suggests that it is worth striving toward these ideals but that we should understand that they never will be reached. He acknowledges that:

"The procedure currently approved in the United States for enlisting human experimental subjects has one great virtue: patient-subjects are put on notice that their management is in part at least an experiment. The deceptions of the past are no longer tolerated. Beyond this accomplishment, however, the process of obtaining "informed consent," with all its regulations and conditions, is no more than an elaborate ritual, a device that, when the subject is uneducated and uncomprehending, confers no more than the semblance of propriety on human experimentation. The subject's only real protection, the public as well as the medical profession must recognize, depends on the conscience and compassion of the investigators and his peers."

Benjamin Freedman agrees--but without dismay--that "fully informed consent" is unattainable and suggests that striving for it is, in most cases, undesirable (32).

He proposes that it might better serve our purposes to negotiate for "valid consent" rather than for "fully informed consent". He concludes:

"...that valid consent entails only the imparting of that information which the patient/subject requires in order to make a responsible decision. This entails, I think, the possibility of a valid yet ignorant consent."

Further: "...the informing of the patient/subject is not a fundamental requirement of valid consent. It is, rather, derivative from the requirement that the consent be the expression of a responsible choice. The two requirements which I do see as fundamental in this doctrine are that the choice be responsible and that it be voluntary."

He sees responsibility as a dispositional characteristic which can be defined only relatively and conditionally in the context of the totality of one's knowledge of an individual. Similarly, he claims that "voluntarism" and reward can be evaluated only in the context of the prospective subject's total environment.

Perhaps germane to the argument presented earlier in the present paper--that it is a serious step for an IRB to impose a requirement for third party scrutiny--are some of the points Freedman makes under the heading "The Right to Consent":

"From whence derives this right? It arises from the right which each of us possesses to be treated as a person, and in the duty which all of us have, to have respect for persons, to treat a person as such, and not as an object. For this entails that our capacities for personhood ought to be recognized by all--these capacities including the capacity for rational decision, and for action consequent upon rational decision. Perhaps the worst which we may do to a man is to deny him his humanity, for example, by classifying him as mentally incompetent when he is, in fact, sane. It is a terrible thing to be hated or persecuted; it is far worse to be ignored, to be notified that you "don't count"."

Freedman's paper is strongly commended to the attention of the reader who is unfamiliar with it; in my view, this paper analyzes in a formal way the sorts of thinking about informed consent that ought to be

going on in IRBs. I shall conclude that in almost every situation, the negotiations for and the documentation of informed consent ought to be less elaborate than the possibilities presented earlier in this paper. How much less elaborate? This should be determined on a protocol by protocol basis (rarely on a subject by subject basis) by an IRB which collectively is aware of the important issues in informed consent (cf, Summary and Conclusions).

Situations requiring no consent

As noted earlier, NIH now requires full documentation of informed consent to retain for research purposes an organ or fragment thereof removed at either autopsy or surgery--even when the procedures themselves are done in accord with usual and customary medical practice. Holder and Levine have examined the legal bases (as presented by the Office for Protection from Research Risks) as well as the expected consequences of this requirement (25). First, they find that this requirement is not justified by any existing case or statutory law. Secondly, they find that this requirement is enormously wasteful of time not only of investigators but also of the physicians who ordinarily negotiate for informed consent to either autopsy or surgery as well as the prospective consentors. Further, the individuals who might be asked to consent to such procedures are those who are about to undergo surgery and the next-of-kin of recently deceased people. It seems inappropriate to the authors to trouble people in these circumstances with the necessity to make decisions that are made to seem much more consequential than they really

are. Finally, in accord with Ingelfinger the authors conclude that what is likely to be sacrificed in the process is the appropriate respect given to the negotiations for informed consent in situations in which they are ethically (and perhaps legally) appropriate. Some situations are identified in which it might be appropriate to negotiate informed consent to retain specimens for research purposes. These situations may be identified by having in common two attributes:

"1) The information to be obtained by the research procedure either will or might be linked to the name of the individual from whom the specimen was removed. If there is no way to link the information to the name of the individual there seems to be no possibility of putting that individual or his next of kin at risk.

"If, and only if, the first attribute is present the proposed research should be reviewed for the possible presence of the second.

"2) The proposed research may yield information having diagnostic significance. In this regard, one should be particularly concerned if the presence of the diagnostic information might expose the individual to liability for criminal action (eg, detection of alcohol or abuse drugs), or might jeopardize his insurance or Workmen's Compensation status or create the potential for civil litigation. Additionally, one should be concerned about the possibility that the information might significantly change the way in which the individual is perceived by himself, his family, social group, employers, and so on (eg, detection of venereal disease)."

The preceding proposal is not to be construed as indicating that surgical or autopsy procedures should ever be done without appropriate authorization by those entitled to give it. However, the debates as to whether consent for medical practice procedures should be more or less elaborate than those for research procedures notwithstanding, in 1975, documentation of the negotiations for consent to authorize autopsy or surgery for non-research purposes is customarily much less formal than

it is when similar procedures are done for research purposes.

It is recognized that standard forms for consent to either surgery or autopsy currently used in hospitals vary greatly in the language. They contain concerning the disposition of organs and tissues. Thus the preceding proposal was made along with a recommendation that (25):

"...the customary practices of the hospital (should be) made explicit on the consent forms. Thus, the standard forms for consent to autopsy might indicate--when appropriate--that it is customary practice... to remove and retain some organs, tissues, and other parts as may be deemed proper for diagnostic, research, or teaching purposes. Similarly, the...form for...surgery might indicate that it is customary to deliver the removed part to the surgical pathologist for diagnostic testing and that in some cases it might be retained for research or teaching purposes before it is destroyed."

There are several other commonly performed types of research activities (eg, study of "left over" blood, urine, spinal fluid, and so on, collected for diagnostic purposes) which may be analyzed similarly to those performed on specimens secured at surgery or autopsy. In general, the same two attributes will suffice to identify those activities for which informed consent seems necessary.

Situations in which informed consent may be either not feasible or detrimental to the interests of the research.

There are some research activities which present considerable potential harm to the subjects but, in which, any informed consent--in fact, the mere revelation that research is being conducted--might defeat the purposes of the research. Most of these activities are categorized in the so-called "unseen observer" type of research most commonly performed by social and behavioral scientists. The purpose of unseen observer re-

search ordinarily is to observe individual or group behavior as it occurs in a natural environment. The potential harms of this research include violations of privacy and confidentiality. Examples of this type of research and the problems it presents were cited earlier (2, at pp. 24 et seq). Problems peculiar to unseen observer research were discussed extensively at a recent conference (33). A concise discussion of the problems presented by unseen observer research may be found in the A.P.A. Ethical Principles (16, at pp. 30-35).

A major unresolved problem may be expressed as a question: How does one establish the authority to proceed with this type of research? Estimates of potential benefits to society--the importance of the knowledge to be gained--are often influenced by various types of political considerations. The author has proposed earlier (2, at p. 55) that one type of research activity that might appropriately be reviewed for ethical propriety at a national level is that in which society is the subject and the risks to society are deemed substantial. Some types of unseen observer research are included in this category--even when the subject is one individual selected and observed without his awareness.

Unseen observer research is not limited to the social sciences. Psychiatrists, psychologists, and others commonly observe the activities of their patients (or subjects) through a one-way glass or by recording (video or audio tapes) their communications, interactions, and other manifestations of behavior. Much research involves examination of school, employment or medical records. However, study of records and most biomedical research (as contrasted with some behavioral and social research)

in which the observer is unseen is not dependent for its successful completion on a lack of the subject's awareness of the observation.

Situations in which documentation of the negotiations seems unnecessary or self-defeating.

In research activities in which it is proposed to do something that will cause the subject only minor to modest inconvenience, that has no potential for causing lasting harm to the subject, and that does not call upon the subject for continuing or repeated involvement, it seems appropriate to negotiate informed consent without the aid of written instruments. In some cases implied consent may be quite sufficient. For example, an investigator may indicate to an individual that he wants a blood sample for purposes of doing some basic research. If that individual offers his arm for purposes of allowing blood to be drawn it may be said that he has granted implied consent. In this situation it is the responsibility of the investigator to inform the subject of anything that might influence his willingness to offer blood. Thus, for example, if there is anything inherent in the research that might meet the two attributes specified for establishing a necessity for informed consent (cf, Situations Requiring No Consent) it is the responsibility of the investigator to so inform the prospective subject. On the other hand, if he merely wants a source of red cell membranes, one would not ordinarily hold him accountable for a detailed explanation of the purposes of his research.

In some types of questionnaire research implied consent seems appropriate. The investigator may distribute copies of a questionnaire by mail along with a covering letter indicating what protections (if appropriate)

are provided for preserving the confidentiality and privacy of respondents. He might further indicate that completion of the questionnaire and its return to the investigator implies consent. When what is being sought are aggregate data on groups, it might, in fact, defeat the purposes of preserving confidentiality by having subject's names on consent forms.

In the conduct of innovative therapy--in emergency situations--it may best serve the interests of the patient-subject to proceed without informed consent. In some cases, the time it might take to negotiate informed consent might delay initiation of the therapy beyond the time during which it would be most effective. To put it most dramatically, the patient-subject might expire during the course of the negotiations. In situations in which the patient-subject is inaccessible owing to unconsciousness or inebriation, it might be feasible to proceed with proxy consent given by the next of kin. However, in true emergencies or when the next of kin is not available it will ordinarily be considered appropriate to proceed without consent. In situations in which the therapeutic innovation is being performed repeatedly in an institution, at the time any particular patient-subject for whom it might be appropriate arrives, the general plans to conduct this activity will have ordinarily been reviewed and approved by the IRB. If the physician-investigator anticipates that the innovative procedure might be used in emergencies or in patient-subjects who are incapable of consenting, he should specify this in the protocol to be reviewed by the IRB. The IRB should develop

clear understandings with the physician-investigator as to the circumstances in which proceeding without consent would be considered appropriate. This process also assures that group judgment will be superimposed upon that of the physician-investigator that the particular innovative therapy is, in fact, the best therapy available for a particular class of patient-subjects.

In some cases it might be considered appropriate for a physician to proceed in an emergency situation with a therapeutic innovation that has not been reviewed by the IRB. It might be that the particular patient-subject is the first in whom the innovative therapy is tried in that particular institution. Alternatively, a physician might conceive of a novel approach to a unique problem. In such situations, the physician should be aware that subsequently he will be held accountable to the IRB for having attempted to meet the standards it might have imposed if consulted in advance. He will also be held accountable to the patient for an explanation of why he assumed that, had the patient been able to give his informed consent, he would have.

Summary and Conclusions

This paper begins with an identification in its first section of seven separate functions that informed consent might be seen to serve. Throughout the paper an attempt is made to relate each of the component processes of informed consent and the devices that might be used to assure the accomplishment of these processes to the various functions specified at the outset.

The author concludes with Katz that informed consent remains an ill-defined concept. In order to prepare the ground for discussing the possi-

bilities of informed consent, there is first a presentation of how it is defined by DHEW regulations and how it might be seen most idealistically by Katz, Jonas, and others. An attempt is made to develop a model that might aspire to these high standards. Yet, later, (pp. 71 et seq) the conclusion is reached that it is almost never necessary to use all of the possibilities presented earlier in the paper. Freedman's proposal that "valid consent" might better serve our purposes than "informed consent" is endorsed by this author. This conceptualization accommodates the possibility of "valid yet ignorant consent".

Informed consent is a type of a contract in which one of the contractors (the investigator)--as in all fiduciary relationships--is held accountable for higher standards of responsible conduct than are most individuals in creating commercial contracts. The negotiations resulting in the creation of this contract are presented as having four component processes. The investigator is assigned responsibility for seeing to it that each of these four processes is accomplished satisfactorily.

The first is that of informing the prospective subject. Eleven essential elements of information are listed in the table of contents on the title page. Perhaps the most important is that of defining the role of subject and how it differs from that of patient (or any other client of a practicing professional). Particularly difficult issues to resolve are presented under elements 5) and 6). Under element 5), the perils of both overdisclosure and underdisclosure are discussed. A most difficult problem is that of determining which information is "material". Definitions of materiality as developed in recent court decisions are presented. Devices

such as the "consent jury" and the "surrogate system" for making decisions as to what information is material are discussed.

In section 6) a major problem is identified. How does one determine the extent to which disclosure of hoped-for benefits other than direct health benefits might be viewed as undue inducements?

Under element of information number 11) it is proposed that in some circumstances it is appropriate to ask a prospective subject to agree to being incompletely informed. However, lying to prospective subjects should be avoided.

Some barriers to comprehension and devices that might be used to overcome them are discussed. In some cases it might be appropriate to use the "two-part consent form" to assure the investigator that the prospective subject comprehends the key elements of information.

Similarly, barriers to autonomy are discussed. It is concluded that any person who assumes the "sick role" is incapable of complete autonomy. The definition of the sick role is deliberately extended beyond that of patient. It is meant to include all individuals who are somehow incapable of performing the roles and tasks for which they have been socialized and who are expected to seek technically competent assistance in "getting well". Some devices are suggested that might aid in determinations as to whether the prospective subject is suitably autonomous; it is acknowledged, however, that one never knows with certainty.

Consent is not seen as the mere consummation of a contract. Rather, it is necessary that the investigator remain sensitive to the possibility

that the subject may wish to terminate the contract at any time.

For the past 30 years there seems to have been nearly universal agreement that negotiations for informed consent to the investigator-subject relationship should meet higher standards than those for the physician-patient (or any analogous professional-client) relationship. However, there have been some recent departures from this viewpoint. Various opposing points of view are presented. The author concludes that patients (or other clients of professionals) are entitled to the same degree of thoroughness of negotiations for informed consent as are subjects. However, the patient (client) should, in general, be allowed more freedom than the subject to relinquish this entitlement. As noted earlier, the subject should be made aware of how the role of subject differs from that of client.

The possibility that supervision of the negotiations for informed consent by consent committees might be advantageous to the participants (and particularly to the prospective subject) is examined in some detail. It is concluded that the best interests of all concerned might be achieved more effectively and at much lower cost through the use of third party scrutiny. There is an identification of the various individuals who might be called upon as third party scrutinizers as well as the situations in which they are most likely to be found useful. It is suggested that the need for third party scrutiny should be proposed by the investigator and reviewed and approved by the IRB. Ordinarily, the prospective subject should be allowed the option to select a third party scrutinizer or to refuse such scrutiny. It is a very serious step

to impose on a prospective subject a requirement for third party scrutiny; often such a requirement is tantamount to a declaration to the prospective subject that his judgment (ability to comprehend; ability or freedom to make choices; and so on) is questionable. However, in some cases such a requirement is necessary.

Attention is directed to existing DHEW and FDA regulations for documentation of informed consent. It is suggested that these regulations are excessively inflexible. The perils of inflexibility are discussed in several subsequent sections. In the section entitled Situations Requiring No Consent several perils are identified of requiring fully documented informed consent in situations where it is not necessary. Most alarming is the dilution and deprecation of the important by a proliferation of the trivial. What is likely to be sacrificed is the appropriate respect given to the negotiations for informed consent in situations in which they are ethically (and perhaps legally) appropriate.

In almost every research activity involving consequential risk or inconvenience to the subject it is most appropriate to document in writing the fact that appropriate negotiations for informed consent have been conducted. The consent form can almost never be so constructed as to anticipate all of any particular prospective subject's wishes to be informed. The consent form is most effective when it is viewed by the investigator as an instrument designed to guide him in his negotiations with the prospective subject. The consent form should contain at least the minimum amount of information and advice that should be presented during the negotiations for informed consent. If any substantive new understandings are

developed in the process of the negotiation which have any bearing on the prospective subject's willingness to participate these should be added to the consent form signed by that particular individual.

The remainder of the issues discussed in this paper are identified by category in the table of contents beginning with page 62. The titles of the sections suggest the conclusions of the author.

At many points throughout this paper it is concluded that the IRB should be assigned responsibility for determining what constitutes the minimum standards of informed consent for each protocol it reviews. This proposal recognizes the impossibility of defining what constitutes adequate informed consent to research generally or even to broad categories of research. Minimum standards determined by the IRB should be set rather high. The IRB should be aware of the perils both of underinforming and of overinforming; when in doubt it should err somewhat on the side of overinforming. The IRB should be so constructed as to collectively be aware of all of the consequential issues in informed consent. It should review proposals drafted by investigators to accomplish the four component processes of the negotiations for informed consent; the personnel who will be called upon to negotiate, consult, or scrutinize the negotiations; the form and substance of the documentation of the negotiations; and so on. Regulations should be developed that will guide the IRB in its deliberations on the issues of informed consent to participation in particular protocols. However, these regulations should be sufficiently flexible to allow a well-informed IRB to meet the needs of particular proposals to do research on particular subject populations.

These regulations should reflect an assumption of trust of the IRB by the regulatory agency. Similarly, the IRB in its dealings with individual investigators should reflect an assumption of its trust of the investigator. It is acknowledged that some investigators have not conducted themselves in their negotiations with subjects in a way that is conducive to developing regulations based on assumptions of trust. However, an awareness of the need to safeguard the rights and welfare of human subjects is gradually pervading the environments in which research is done. A changing social consciousness in the research environment is diminishing the probability that "permissive" (34) investigators will escape notice; in the current environment they are more likely when noticed to be reprimanded than rewarded. Regulations based on assumptions of trust are far less costly--financially, but even more importantly, socially--than are those based on assumptions of distrust.

Finally, it is concluded that the nature and definition of informed consent cannot be described definitively in the abstract. Functionally relevant definitions can be developed only in relation to specific proposals. In each case, the investigator should draft his proposal based on his knowledge of all aspects of the research and of the prospective subjects. The IRB should review the plans and negotiate with the investigator what has been referred to as the minimum standards for that particular project. The investigator should then proceed to negotiate with prospective subjects with an awareness that the plan he has agreed to with the IRB may often have to be supplemented or modified to meet the needs of particular subjects. Thus it is that the nature and definition

of informed consent is and ought to be continually negotiated and re-negotiated.

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APPROPRIATE GUIDELINES FOR THE SELECTION OF HUMAN
SUBJECTS FOR PARTICIPATION IN BIOMEDICAL
AND BEHAVIORAL RESEARCH

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The Commission is charged with the responsibility to consider: "Appropriate guidelines for the selection of human subjects for participation in biomedical and behavioral research." This paper is an attempt to identify and to begin to analyze the issues that must be considered as one attempts to respond to this charge. The following assumptions limit the scope of this paper: It is assumed that the reader will be familiar with the three previous papers prepared by the author for the Commission (1-3); some of the concepts developed in this paper will be incomprehensible without reference to the previous papers. Separate papers are being developed for the Commission on research involving children, prisoners, the institutionalized mentally infirm, psychosurgery, and the role of the research subject as a job. Since it is assumed that these papers will deal with guidelines for selection of subjects in and for these categories, this paper will address only to a limited extent problems peculiar to these populations.

The paper begins with a statement of a principle for defining the universe of prospective subjects for any particular research proposal according to the biological and/or social attributes necessary to test the hypothesis of the proposal. This principle is meant to have priority over any subsequently stated guidelines. There is next a classification of various types of research according to three separate sets of criteria. First, a separate class is developed as one that presents mere inconvenience to individual subjects as opposed to true risk of harm. Next there are three categories of research which present either known or unknown risks of physical or psychological harm to individual research subjects. A final classification is one that presents risks to groups or classes of subjects. In this section there is a draft of some guidelines for selection of subjects which are oriented primarily toward minimization of harm to either individuals or groups of individuals. The remainder of the paper is concerned with selection of individual

subjects with a view toward protecting the rights and welfare of individuals.

The next section is concerned with a classification of prospective subjects. Particular attention is devoted to identifying those who might be incapable of protecting their own rights and welfare by virtue of being either uncomprehending, vulnerable or dependent. In this section, further guidelines are proposed which are designed to assist such persons in the protection of their own rights and welfare. In some cases it is acknowledged that some persons are absolutely incapable of protecting their rights and welfare even with assistance; this responsibility must be assumed by others.

In the next section there is a reexamination of the various categories of research which present either inconvenience or risk to individual subjects. There is little further discussion of the protection of the interests of groups except in situations in which groups might have desired dependency statuses threatened. The purpose of this section is to examine some special cases of research presenting either known or unknown risks of physical or psychological harm to explore the conditions under which various sorts of subjects might be selected.

It is suggested that establishment of a suitable system of compensation for harmed research subjects would yield a variety of salutary effects including the facilitation of the development of satisfactory guidelines for the selection of subjects for research presenting risk of physical or psychological harm.

The concepts of community consent and consultation, surrogate consent and consultation, lottery systems, and reciprocal obligation, are each discussed in detail at the first point in the paper at which it appears it might be useful in developing guidelines for selection of subjects (cf, Table of contents).

In general, an effort has been made to open for discussion a reasonably comprehensive list of issues that must be considered in developing appropriate guide-

lines for the selection of subjects. In some cases there are proposals for the language that might be used in guidelines the Commission might wish to recommend. Some of these are presented in language that is more definitive or more demanding than the realities of research (or society) may be able to accommodate. More commonly, there are presentations of general formulations that might lead to the development of guidelines. Some difficult problems are identified which one might wish to attempt to resolve through guidelines without proposed guidelines or general formulations; in general, this reflects an attitude of pessimism on the part of the author that such problems are susceptible to resolution through guidelines.

SELECTION BY REQUIREMENTS OF THE RESEARCH

Principle: The subjects of research shall have those attributes that will permit adequate testing of the hypothesis. In most biomedical and in some behavioral research the attributes can (and should) be stated precisely in biological terms. In some behavioral and in most social research, the attributes can (and should) be stated in social terms. An adequate statement of those biological and/or social attributes that establishes a universe of prospective subjects includes criteria for exclusion as well as inclusion.

This principle is derivative on a conclusion developed in a preceding paper (2, at pp. 29-31):

"...There is no way to separate the issue of quality of scientific design of research from the ethical considerations as to whether it should be done. If research is badly designed it is not likely to benefit anyone. Thus, it seems inappropriate to put human beings at risk to develop information (or misinformation) that cannot conceivably benefit either the individual or society."

This principle has far reaching implications in the protection of human beings. It not only protects the rights and welfare of the individuals who are the subjects of the research. Much harm can be done by including in the subject population in-

dividuals who are not legitimately part of that population. The most grave consequences of this sort of inappropriate selection of subjects may be seen when the purpose of the research is to develop a diagnostic test or a form of therapy for a condition. Owing to improper selection of subjects, the efficacy of a diagnostic test or therapeutic modality may be either overestimated or underestimated. A means to diagnose or treat a condition may be inappropriately utilized by others (those who read the results of the research) who may be unaware that they are applying it to individuals differing in important respects from those who were subjects of the research; for an exhaustive discussion of the problems deriving from inappropriate or inadequate definition of the biological attributes of research subjects see Feinstein (4).

In a recent editorial commenting on the remarkably divergent results of various surgical and other approaches to treatment of patients with unstable angina, Pauker asserts (5):

"The variation in the prognosis of patients with unstable angina is due, in part, to disparate definitions of acute coronary insufficiency and to differences in the degree of coronary obstruction." Consequently, providing a patient "...with meaningful, objective data about his prognosis is a difficult task since the literature is replete with conflicting studies and since prognosis depends on the availability of necessary resources and upon the skill of the physicians and surgeons."

Our ability to define categories of people in biological terms changes with time. Seemingly homogeneous categories tend to become heterogeneous. Thus, 40 years ago--based on the understandings of the time--it would have been appropriate to study a form of therapy for hypertension. Now that we know that hypertension is not a disease but rather a manifestation of a large number of diseases such a study would be inappropriate.

In 1975 it is necessary to develop a subject population that may be adequately

described either as having essential hypertension or as having hypertension due to some specific cause. Within the population of those with essential hypertension it is customary to subdivide groups for study according to certain parameters that can be defined more or less precisely. Thus, a study may be done on the effects of a certain form of therapy in a population described as having mild, moderate, severe, or accelerated hypertension. These groups may be further subdivided as having or lacking various specific complications; eg, renal, cardiac, or cerebrovascular. At the time of this writing there is considerable controversy as to whether each of these groups ought to be further subdivided on the basis of whether their plasma levels of the enzyme, renin, are high, normal, or low.

About 15 years ago it was considered appropriate to categorize all children having certain behavioral attributes as hyperkinetic or, alternatively, having one homogeneous category of minimal brain dysfunction (MBD). Trials of various forms of drug therapy and psychotherapy in various locales yielded remarkably divergent results (6). Furthermore, the prevalence of MBD in various grammar schools was reported as ranging from less than 1 per cent in some suburban schools to greater than 30 per cent in some inner-city schools. With time it became apparent that certain environmental factors could produce behavior that was difficult to distinguish from MBD. For example, it was found that hunger--particularly going to school without having had breakfast--could produce such behavior in some children. Some children who were being taught by teachers who did not share their primary languages also manifested such behavior. Correction of these environmental factors was associated with a sharp reduction in the apparent prevalence of MBD. Children in whom the diagnosis was established on the basis of improved criteria were much more likely to respond favorably to treatment

with drugs that stimulate the central nervous system (eg, amphetamine). There was a corresponding decrease in the frequency with which central nervous system depressants (eg, barbiturates and major tranquilizers) were considered necessary owing to failure of stimulant drugs. All of these revised understandings functioned to benefit the children. For example, it must now be unusual that hungry children are heavily sedated in order to control hyperkinetic behavior (or--as the media of the time suggested--drugged into submission).

In many studies it is necessary to include in the subject population individuals who are commonly called "normal controls" or "healthy volunteers". There are no such persons. Normality and health are states of being that cannot be proved scientifically. Thus, it is ordinarily preferred to describe these individuals as being free of certain specific attributes of non-health or non-normality.

In an earlier paper (1, at pp. 7-8) some examples were given from biomedical and social research of studies in which it would have been either impossible or self-defeating to define precisely the prospective subject population in advance. It was also pointed out that the criteria for selecting subjects may quite properly evolve during the conduct of research as a consequence of the early research findings.

RESEARCH CLASSIFIED BY NATURE OF RISK

In this section research will be classified in five more or less distinct categories. These categories are defined first by the nature of the risk and second by whether the major burden of the risk is borne by an individual subject or by the class of persons whom he represents.

First, it will be necessary to distinguish inconvenience from physical or psychological harm. There seems to be a widespread assumption that most research

imposes on subjects a substantial risk of harm. In the view of the author this assumption has been created by the fact that those categories of research that have the greatest potentials for harm are those that have been most widely discussed in media addressed to the public. It is equally fair to state that there are other imbalances in the public's conception of the relative harms and benefits of some sorts of innovative practices; eg, overly enthusiastic reports of new therapies at times mislead the public to thinking that they are better than they are. Some persons (prospective subjects) may believe inappropriately that merely because a form of therapy is novel or experimental it is somehow better than those in customary use (7).

The first category of research is: 1) Research presenting mere inconvenience to the subject. The next three categories of research are those presenting a possibility or probability of physical or psychological harm to individual subjects; these are: 2) Research presenting unknown risk of physical or psychological harm; 3) Research presenting known risk of physical or psychological harm; and 4) Research presenting combinations of known and unknown risk. Most innovative therapy (practices) will be found in categories 2 and 4. The final category is entitled: 5) Risks borne by society, institutions, or classes of people. Research conducted in this category presents risks to groups of individuals considered as groups. The risks in this category are not only physical and psychological, they may also be social, economic, and legal. The research conducted in this category may be basic biological, biomedical, behavioral or social. Guidelines are proposed for this category that are designed to minimize harm to the group.

1) Research presenting mere inconvenience to the subject

Inconvenience is defined (15) as a noun: "2: Something that is inconvenient: something that gives trouble, embarrassment, or uneasiness: something that disturbs or impedes." Inconvenient is defined as an adjective: "2: Not convenient: giving trouble, uneasiness, or annoyance: Disadvantageous, inopportune."

Research which presents the subject with the necessity of bearing the burden of mere inconvenience is distinguished from that which presents the possibility of consequential injury (determined as a function of probability and magnitude). Research in this category employs techniques, modalities, and interventions that have been tested sufficiently to earn the classification (by the social device) of accepted or approved (for either research or practice purposes) (1, at pp. 5-6). Research presenting mere inconvenience is characterized as presenting no greater risk of consequential injury to the subject than that inherent in his particular life situation. In determining the risks inherent in the particular life situation of a prospective subject, it is not appropriate to consider risks irrelevant to the design or purpose of the research; thus, for example, in considerations of the risks of most biomedical research with a view toward categorizing proposed research as presenting mere inconvenience (as opposed to harm) it is inappropriate to enter into the calculations the risks of being injured in an automobile accident.

The various inconveniences of participation in research have been described in earlier papers (1-3). In general, what is asked of a prospective subject is that he give his time (to reside in a clinical research center, to be observed in a physiology laboratory, to fill out a questionnaire, to be interviewed, and so on). Often there will be a request to draw some blood or to collect urine

or feces. Certainly, the withdrawal of venous blood may be momentarily painful and be followed by a bruise but no lasting physical harm is done. Removal of some other normal body fluids may be associated with some risk of substantial harm; eg, brain fluid, heart blood. Ordinarily, it is possible to do such studies in individuals who require removal of heart blood or brain fluid for diagnostic or therapeutic purposes. In these cases the fact that some of the fluid is removed for research purposes imposes no additional risk or inconvenience on the subject. Removal of abnormal fluids or tissues can only be done on those who have the diseases associated with the development of these abnormal fluids (pleural effusions) or tissues (eg, tumors). Again, in such persons, the interests of research and practice usually may be served simultaneously. Removal of normal body tissues may or may not present a risk of physical harm or inconvenience. Thus, removal of a piece of skin by standard biopsy procedures is associated with minor discomfort lasting about 7-10 days in suitably selected individuals. On the other hand, biopsy of the liver is associated with a probability of approximately 0.002-0.005 of complications sufficiently serious to require treatment (eg, blood transfusion) and of approximately 0.0002 of death. Thus, the performance of a liver biopsy cannot be considered an inconvenience, when this is done for research purposes it must be considered in category 3): Research presenting known risk.

Some normal tissues are obtained as by-products of indicated surgery. It is customary surgical practice to remove a margin of normal tissue around the diseased tissue to assure complete removal of a tumor or of an infection. Thus, it is ordinarily possible to get specimens of most normal tissues without even causing inconvenience to the individual (for purposes of these con-

siderations I would not even call this individual a subject unless the two attributes specified earlier exist (3, at pp. 76-77).

As was noted earlier (2, at pp. 15-19) many types of social, behavioral, and biomedical research present the potential for social, legal, and economic risk to the subject. An attempt to reduce the probability of economic risk to the individual is presented subsequently (cf, Compensation). The remainder of the risks in this category usually will not become manifest as harm unless there are violations of confidentiality. In most cases, safeguards of confidentiality can be established to the extent that all concerned can be very confident that there will be no violations. Thus, most research dealing with confidential information can be considered as presenting mere inconvenience. Of course, there are exceptions; where there are barriers to preservation of confidentiality--legal or otherwise--the research might be considered as presenting known risk.

General formulation for guidelines: In research presenting social or legal risks to the individual which might become manifest through violations of confidentiality it is the responsibility of the investigator to inform the prospective subject of the extent to which confidentiality can be assured. If the investigator can assure absolute protection of confidentiality the research is to be considered as presenting mere inconvenience. In such cases the investigator assumes responsibility (liability) for any social or legal harm done to the subject as a consequence of failure to maintain confidentiality.

If there are barriers to preservation of confidentiality, these should be disclosed to the prospective subject. The prospective subject assumes the risk of the consequences of violations of confidentiality through mechanisms of which he has been forewarned.

2) Research presenting unknown risk of physical or psychological harm

It is often stated and indeed has been in this series of papers (1-3) that any time we intrude a chemical, device, or other intervention upon the body or personality of an individual there is an element of uncertainty as to the outcome (both harms and benefits). However, some interventions have been performed sufficiently often in conjunction with detailed observations of their harms and benefits so that we are able to predict statistically what the effects will be of their repeated performance in a population very similar to that in which safety and efficacy were established. It will almost always be more difficult to predict what their effects will be in any individual member of that population. This sort of unknown is not the category developed in this section.

The category defined in this section is characterized as follows: The technique, modality, or intervention has not been performed sufficiently often or sufficiently well in humans to permit a reasonable assessment of the probability and magnitude of harm it might produce. Some innovative therapy (practice) is contained in this category. In cases of innovative therapy it may also be said that the modality has not been tested sufficiently to provide a reasonable assessment of its relative efficacy. As noted earlier (2, at p. 5a):

"...When a relatively new drug is used experimentally in the treatment of a disease for which there exist other proved drugs, one of the risks involved is that for the duration of the study the subject will be deprived of the benefit of the proved drug. It may well be that the experimental drug will prove to be superior to the proved drug; however, this cannot be assumed during the course of the experiment."

When a modality that has been tested previously in one class of humans--

sufficiently well to merit the social classification of accepted or approved-- is tested for safety and/or efficacy in another class of humans, the activity is classified in category 4): Research presenting combinations of known and unknown risk.

It should be emphasized that a specific modality (drug, device, surgical procedure, psychologic test, and so on) should rarely be classified as either a research or practice modality. Modalities that have been sufficiently well tested to merit the social classification of accepted or approved may still be employed with either research or practice intent. Thus, for example the procedure of liver biopsy was discussed in the preceding section. When a liver biopsy is performed for purposes of diagnosing hepatitis, this activity is practice. When the same procedure is employed to secure a specimen of liver to determine the level of some enzyme in normal subjects (normal in that they are free of evidence of liver disease) this is research. When a new device is used to secure a specimen of liver from a person who is thought to have hepatitis with the expectation that it will be possible to establish a diagnosis based upon the availability of that liver specimen, the procedure is classified as innovative therapy (practice).

3) Research presenting known risk of physical or psychological harm

Research considered in this category employs techniques, modalities, and interventions that have been tested sufficiently well to predict with reasonable certainty both the probability and magnitude of physical or psychological harm in the prospective subject population. In the case of prophylactic, diagnostic, or therapeutic maneuvers, they have been tested sufficiently well to be classified as accepted or approved by the social device.

The probability and/or magnitude of physical and psychological harm is greater than that inherent in the subject's life situation.

Beecher (8, at pp. 127-128) has provided statistics on estimated death rates from procedures that might be done with either practice or research intent. Among the procedures for which he provided data were cardiac catheterization, liver biopsy, and general anesthesia. His estimates--prepared six years ago--are probably high for 1976. However, they do show that such data can be developed and I agree with him that they should be developed in order to assess the risks of doing research. In a previous paper (2, at pp. 49-53) there was presented an account of what constitutes an adequate description of risks and benefits. It was pointed out that it is ordinarily possible to predict which sorts of subjects would be most susceptible to developing known harms of research procedures. It was further pointed out that "...potentially irreversible harms, if detected early, may be either avoided entirely or reduced in magnitude. This avoidance or reduction may be accomplished by discontinuation of the potentially harmful research procedure. Alternatively, minimization of a developing or nascent harm may be accomplished by therapeutic interventions; eg, timely administration of an antidote to a 'poison'."

Deriving upon the immediately preceding discussion, three general guidelines may be formulated; the purpose of each is to minimize harm. The first 2 are equally applicable to research in categories 2 and 4; the facilities requirement in the third is too stringent for most category 4 activities.

a) Guideline: Every possible effort should be made to convert known risk of physical or psychological harm to mere inconvenience.

Illustrative examples: In a person having a tumor for which the administration of methotrexate is indicated, studies on the metabolism or biological effects of methotrexate may be categorized as presenting mere inconvenience. On

the other hand, administration of methotrexate in therapeutic doses to an individual for whom it is not indicated for purposes of performing the same studies presents a high probability of serious physical harm. See also liver biopsy examples in preceding section.

b) Guideline: Utmost effort must be made to identify those individuals most susceptible to harm for purposes of excluding them from the prospective subject population.

Illustrative examples: In research designed to test the effects of strenuous exercise in "normal" humans, one would ordinarily plan to perform various screening tests to identify individuals with coronary artery disease in order to exclude them. In planning research involving kidney biopsies, utmost effort must be made to identify those individuals most susceptible to the serious complications of the procedure; eg, those having hypertension, bleeding disorders, solitary kidneys, and so on.

c) Guideline: Research should be conducted only by investigators who are highly skilled in the early detection and minimization of developing or nascent harms. The facilities immediately available to them to accomplish these purposes should be the best known.

4) Research presenting combinations of known and unknown risk of physical or psychological harm.

The most important type of research in this category is innovative therapy in which the therapy has been proved safe and effective in one human population and which is to be tested for safety and/or efficacy in another. According to our current customs, this type of activity is most commonly conducted formally when the innovation is a drug. However, as noted earlier, this can also be the

case when the innovation is a surgical, radiological or other procedure (1, at pp. 13a-16a). In general, there are two broad subsets of this category of research. The first is that in which the modality has been proved safe and effective for the treatment of a certain disorder in one class of humans but which is now to be used in the therapy of the same disorder in another class of humans. The differences in these classes of humans are determined by such biologic attributes as age, sex, pregnancy, and altered states of physiology that are either induced deliberately (eg, by co-administration of another drug) or are naturally occurring (eg, coexistence of another disease). The second broad subset is that in which a modality proved safe and effective in the therapy of one disorder is now to be tested for efficacy in a dissimilar disorder.

In general, in making decisions on selection of subjects for research in these categories it should be assumed that at least the same degree of harm will be manifest in the new subject population as was in previous populations. Thus, the three guidelines for minimization of known harm presented in the preceding section should be applied. It should also be understood that there may be additional harms yet to be discovered.

The two subsets developed in this category differ most importantly on the matter of assumptions of direct health-related benefit to the subject. In general, it may be assumed that when the same modality is used to treat the same disorder in persons who are biologically different from those in whom its efficacy was established, equivalent direct health-related benefits will accrue to the new population. This is stated as a general assumption which is not perfectly true. Many examples can be cited, for example, of altered states

of physiology induced by diseases, prior ablation of some organ, or coadministration of some drug that will either partially or totally inactivate a drug. However, most of these situations are either known or capable of being predicted. Undoubtedly, there will be additional surprises in the future. However, the general assumption of equivalent benefit seems to be justified.

In a subsequent section (cf, Research presenting combinations of known and unknown risk--2) guidelines will be developed for selection of subjects for this subset of research. Based on the general assumption of equivalent benefit as well as the assumption of nearly equivalent risk (this assumption will be developed further in the same section) it will be proposed that most persons will be in a highly strategic position to express their personal choices as to whether they wish to become subjects of this sort of research.

On the other hand, in cases in which a therapeutic modality is being studied for efficacy in the treatment of a disease other than that for which it is accepted or approved, the assumption of equivalent benefit does not obtain. This will lead to the development of a guideline for the selection of subjects for this subset that is more limiting than that for the preceding subset.

5) Risks borne by society, institutions, or classes of people.

It is proposed that when it is a group that will be put at risk, informed consent should be obtained from the group as a group. The process through which this is accomplished will be called community consent.

Community consent is defined as informed consent negotiated with the community in which it is planned to conduct research or from which it is planned to draw prospective subjects. The elements of informed consent to be negotiated

with the community are each of those eleven (3, at pp. 9-31) that are germane to the proposed research. It is reemphasized that the process of creating a condition which may be called informed consent is to be considered a negotiation; in this case the negotiation is to be between the investigators and the community. During the process of these negotiations it is quite possible that some aspects of the proposal might be modified; this may be documented as was suggested for negotiations for informed consent with individuals (3, at p. 58).

The functions of community consent are essentially the same as those cited earlier for informed consent; these were listed in an earlier paper (3, at pp. 2-4) and have been elaborated in detail by Katz and Capron (7, at pp. 82 et seq). However, in some situations requiring community consent, different functions may be given greater or lesser weight. Thus, for example, it will be seen that in negotiating informed consent for most social policy research, it will be impossible to honor the first function of informed consent: "To promote individual autonomy".

The community may consent to overriding the necessity for individual informed consent to several categories of research. These include social policy research which requires arbitrary allocation of material goods and saturation involvement of the community as well as research involving some types of inconvenience. The community may not consent to imposing known and/or unknown risks of physical or psychological harm on one of its members without the consent of that member. Community consent will also be recommended for some categories of research to be conducted in groups of subjects having dependent relations to institutions when their selection is based primarily upon their being administratively available (cf, Dependent subjects and Randomized clinical trials). In general, in these cases the community will be offered the option to refuse to consent to some aspects of the proposal.

Community consultation is to be distinguished from community consent. Community consultation involves consultation with the community in which it is planned to conduct research or from which it is planned to draw prospective subjects. In general, the function of community consultation is to assist the investigator in learning how to better conduct his negotiations for informed consent with individuals within the community. In cases in which individuals are asked to assume known or unknown risk of physical or psychological harm and in which the potential benefits are expected to accrue more to the class of persons than to the individual research subjects, through community consultation it may be learned whether the class perceives the potential benefits as being worthy of assuming the risks of research even by a small proportion of their class. Another purpose of community consultation will be to reduce the fragility of individuals who are either highly vulnerable or highly dependent (cf, Dependent subject). Community consultation will also be advised for establishing lottery systems (cf, Lottery Systems).

Various procedures may be used to negotiate community consent or to achieve community consultation; some of these will be detailed in relation to specific categories of research for which the procedures seem most appropriate.

Social policy research

Some activities in this category were discussed briefly in a preceding paper (1, at pp. 20-25). This special case of research presenting risks to groups will now be reviewed in greater detail.

Veatch (9) has recently surveyed some of the problems inherent in con-

ducting social policy experimentation. He defines this as "conscious and systematic experiments designed to yield results useful in the formulation of public policy, where this intervention involves a sample of the human population and sometimes a control group." He explores the ethical issues in this field in relation to established and developing ethical principles for biomedical and behavioral research.

In social policy research, one maneuver that may be performed is the arbitrary allocation of material goods (cash, food, shelter, education, and so on) to one segment of the population and measuring in some formal way the effects of such allocation on the recipients. Simultaneously, a control group that is as similar as possible is studied to see how well they fare without having been recipients of the material goods. Veatch contends-- and I concur--that members of the control group are equally subjects of the social policy experiment. Thus, in some respects this type of research is analogous to the randomized clinical trial (RCT) (10). However, in some respects it is clearly very different.

As Veatch observes (9, at p. 53): "Social policy research may be quite a different matter. Subjects may be assigned to treatment groups before being contacted for enrollment. It is impossible to disguise the nature of the treatment as is normally done in medicine. Subjects in social policy research know in advance whether they are in the control or treatment group.... Systematically transmitting such information would eliminate some of the problems of accidental discovery. Certainly the community approving agency (such as the city council) would have to know of the different treatments. That information should not be withheld from the subjects."

Veatch further proposes (9, at p. 47): "A critical element in gaining legitimacy for such research is community consent openly arrived at (emphasis added). This of course raises serious problems of determining who speaks for the community and what would constitute a valid consent, problems that are being faced in society generally. The most closely analogous problem in medicine is in the establishment of pilot community-wide programs for genetic screening.

In pilot programs where efforts have been made to elicit broad-based community support (such as in the Tay Sachs screening program in Baltimore), problems have not arisen; in other programs (including some testing for sickle cell disease and traits), failure to obtain community consent has generated hostility."

Further (9, at p. 55): "Responsibility for harm done in social policy research is a complicated problem. Most social policy research will probably have beneficial consequences for most of the subjects at least in the short run. Certain harms will be pervasive, extremely difficult to define. There may well be psychological risks and long-term harms, but these will be nearly impossible to measure and prove. In a school voucher program a child may do worse in the school his parents choose than in the one he was assigned to; in a sterilization incentive test a participant may lose part of his family through death or divorce; in a housing experiment, readjustment problems may make a new neighborhood less attractive than the old. On both moral and practical grounds any individual or agency undertaking social policy research must face the question of responsibility for such possible consequences."

Further (9, at p. 55): "In social policy research, serious harm can come from stopping an experiment. In housing allowance programs the subjects may have abandoned their low-rent and possibly rent-controlled apartments; in health insurance tests, cancelled their insurance; in educational experiments, destroyed the older school systems; in income maintenance experiments, committed themselves to installment payments or to a standard of living from which it would be psychologically difficult and possibly harmful to retreat."

Further (9, at p. 57): "While in medical research return of the patient to his former condition would be clearly unacceptable, in social policy research this is not unthinkable. Social policy research seems to treat subjects much as normal volunteers would be treated in medicine. In both cases there would seem to be a moral claim to restore the subjects' prior condition to the extent possible. This must mean that social policy research subjects, while they are thought to be in need of intervention to improve their lot (as sick patients are), are not thought to be entitled to being maintained in the improved condition that the researchers temporarily place them in."

Finally, (9, at p. 58): "In social policy research the claim of the right to participate in experiments could be a serious problem. The high potential personal benefit from participation together with arguments of justice and fairness produce a strong case for inclusion. Since all people of the affected class can not be included initially (or the research objective would be defeated), the selection principle must be based on some ethically defensible argument." Unfortunately, Veatch does not specify what ethically defensible arguments might be used to establish the selection principle.

It seems quite appropriate to appeal to principles of justice and fairness to determine the right (liberty?) of persons to participate in research

particularly when they consider such participation beneficial. Subsequently, I shall appeal to similar principles in distributing the risks and benefits of certain categories of biomedical and behavioral research. As noted earlier, the universe of prospective subjects for most biomedical and behavioral research is determined according to biological attributes. In developing a theory of justice as fairness, Rawls (11, at p. 104) suggests that native assets (biological attributes) are distributed according to a "natural lottery". An attempt will be made to demonstrate that if this concept is accepted it might be appropriate to distribute risks and benefits according to a man made lottery (cf, Lottery Systems).

There are those who argue that social positions and classes are not distributed according to a natural lottery; rather, these exist as a consequence of the deliberate acts of individuals and institutions. Thus, it may be argued that it is less appropriate to distribute material goods within various social classes according to a man-made lottery. However, as Rawls has observed (11, at p. 96): "The basic structure of society...favors some starting places over others in the division of the benefits of social cooperation." Entry into some social classes may also be influenced by biological attributes. Thus, for example, persons who are less strong or less intelligent may be more likely than others to be on welfare. Similarly, owing to various unjust practices in our society, certain persons may be over-represented in various social classes on the basis of such biological attributes as race and sex.

Social policy research differs from most biomedical and behavioral research in that it often depends upon saturation involvement (9). That is to say that it is simply not feasible to conduct most sorts of social policy research without involving all or nearly all persons in the community having

the social attributes necessary to test the hypothesis. Thus, in most research of this sort the concept of individual informed consent is irrelevant. What is required in its place is community consent.

I have expressed my uncertainty as to whether it is appropriate to distribute material goods within a population according to a lottery. Thus, I shall suggest that it is inappropriate unless the community elects this mechanism for distribution. I shall assume that during the process of negotiating consent with the community, the community will be able to find no more fair or just mechanism for arbitrary allocation of material goods than a lottery.

Guideline: In social policy research involving the arbitrary allocation of material goods to one segment of the population and measuring in some formal way the effects of such allocation on the recipients, community consent is required. If there are control subjects (individuals who will be similarly studied but who will not receive the material goods) they are to be considered part of the community from which consent is required. The elements of information to be conveyed to the community are each of those eleven elements described earlier (3, at pp. 9-31) that are germane to the proposed research.

Procedures for negotiating community consent

1) Ordinarily, the first approach to obtaining community consent for social policy research should be contact with those leaders who are authorized to speak on behalf of the community. In general they should be persons who have been selected by the community according to a democratic process and who are held accountable for their actions to that community. When no such persons exist it may be appropriate to call a meeting of the community from which consent is

desired. Commonly, even when legitimate spokespersons for the community exist, they should be encouraged to call a meeting of the community for purposes of considering the proposed research.

2) The community should agree to rules of procedure for making decisions before it proceeds to make any decisions. For example, determinations as to what constitutes a quorum, what percentage of a quorum must vote yes to each aspect of the decision making, and so on, must be settled before the community determines whether it wishes to participate in the research and, perhaps most importantly, how those individuals who will receive the goods are to be selected.

It will be assumed that the communities to be studied are selected on the basis of their being as nearly identical as possible in their possession of the social attributes that will permit testing of the hypothesis. Therefore, it should be a matter of no interest to the investigators which group will serve as controls. In some cases it might be appropriate--in the interest of opening opportunities to the receipt of goods more widely--to involve more communities in the consent process than one actually intends to conduct the research in. Thus, if one wishes to compare one community with another--the second serving as control--and if one conducts the negotiations for community consent with five communities, each of the five will be presented with a 20 per cent probability of reaping the short-term benefits. Similarly, each will have a 20 per cent probability of assuming the inconvenience of serving as controls.

I shall assume that the community (or collection of communities) will be unable to discover any mechanism for allocation of the goods that they will agree is more just than a lottery. I shall further assume, that since the investigators will

have no interest in which communities are selected as experimental or control that they should be assigned responsibility for conducting the lottery.

During the negotiations with the community for informed consent, the overall purpose of the research should be presented (element of information No. 1); if the purpose is anything other than achievement of a more just distribution of material goods within the society, I shall assume that the community will not consent to participation. Similarly, if there exists any a priori reason to believe that an experimental social policy will not be implemented even if it proves to be safe and effective, there is no ground for justification of the experiment.

Other research presenting risks to society, institutions, or classes of people.

In an earlier paper the risks that might be borne by society were categorized (2, at pp. 19-29). It was observed that the Commission had already determined that some of these risks were so substantial that some categories of research in which these risks were presented should be reviewed for ethical propriety at a national level. These were two categories of research on the fetus (2, at p. 54). It was further observed that DHEW regulations required similar review of research involving in vitro fertilization. It was further proposed that two additional categories might be considered for similar review: The first is that sort of activity in which society is the subject and the risks to society are deemed substantial. The second was that in which the risks might be borne by subsequent generations. Thus, one might include in this latter category research and development procedures that might lead to pollution (broadly defined) of the environment or to genetically-determined anomalies. It was further noted that research not involving human subjects may put society at risk (2, at p. 19). Evidence was presented that in some

cases scientists were assuming responsibility for control of such activities.

Under the rubric of social risks (2, at pp. 20-22 and 24-27) some other types of research are described in which the risks to the group in the aggregate may be considerably greater than might be perceived by any individual member of the group. Thus, one may question whether it is appropriate to ask an individual to consent to participate in research the findings of which might harm the group of which he is a member.

As noted earlier (2, at p. 21), there may be differences of opinion within a group as to whether the results of research were harmful or beneficial to the interests of that group. The determination as to whether it is appropriate to proceed with research of this sort may commonly be a political rather than a scientific decision.

Guideline: In research that presents risks to society, institutions, or classes of people, community consent is required.

The nature of the research is nearly irrelevant; it may be basic biological, behavioral, or social research. The main criterion for establishing this class of research is that in the view of the IRB either: a) The risks to the group in the aggregate are greater than are likely to be perceived by any individual member of the group; b) There is likely to be difference of opinion within the group as to whether the results of the research might be detrimental to the group.

In this category of research there is usually a requirement for negotiating informed consent with each individual. This requirement may be waived only if both of the following requirements are met: a) There is no consequential risk

of physical or psychological harm to any individual; and b) The group according to its own established rules of procedure determines that there is no necessity for each individual to consent.

As noted earlier (3, at p. 3) the functions of informed consent include "To encourage self-scrutiny by the physician-investigator"; "To encourage rational decision making"; and "To involve the public". All of these functions may be served by negotiating for informed consent with the community in this category of research. The investigator may find that there are greatly varied perceptions of the purposes of the proposed research; in that case he might wish to revise it so as to make its purpose seem more clear to the community he wishes to study. Similarly, if the validity of the research is dependent upon the cooperation of individual members of the community--eg, as in the case where they might be asked to complete a questionnaire--even if the community consents to the conduct of the research by a narrow margin (eg, 55 per cent), the results of the study are likely to be invalid owing to sampling bias. In this case it might be predicted that 45 per cent of the prospective subjects would either not complete the questionnaire or deliberately distort their answers to achieve their own purposes.

Undisclosed purpose research

In some studies it is necessary to inform the prospective subject that some information is being withheld deliberately (3, at p. 30). Such studies are most commonly found in the realm of behavioral and social research; however, examples were also provided of biomedical research dependent upon non-disclosure of the purpose.

Veatch has suggested (9, at p. 52):

"In those rare, special cases where knowledge of the purpose would destroy the experiment (and only in those cases), it might be acceptable to ask a group of mock subjects drawn from the same experimental population if they would consent to participate in the experiment knowing its purpose. If there is substantial agreement (say, 95 per cent), then it seems reasonable to conclude that most real subjects would have agreed to participate even if they had had the information that would destroy the experiment's validity."

This proposal seems to combine some of the elements of the surrogate system proposed by Fost and the consent jury proposed by Hauck to which I have alluded earlier (3, at pp. 20-21).

Surrogate consent

Surrogate consent is defined as informed consent negotiated with a group of individuals that is in all important respects (biologically and/or socially) virtually identical to the actual proposed research subject population; in this regard they are distinguished from the surrogates to be contacted for surrogate consultation (infra). The elements of informed consent to be negotiated with the surrogates are each of those eleven that are germane to the proposed research. Surrogate consent is said to have been achieved when a sufficient number of surrogates (say, 95 per cent) state that given full information they would have consented to become research subjects. In contrast to community consent, surrogate consent can never be used to authorize research in the absence of individual or proxy informed consent. However, based upon the availability of surrogate consent, the IRB may decide that it is permissible to proceed with some categories of research without individual or proxy informed consent; eg, unseen observer research.

Surrogate consultation is distinguished from surrogate consent in that the surrogates are not virtually identical to the actual proposed subject popu-

lation. Surrogate consultation is used in cases in which community consultation might be desired but the actual proposed subjects are either too uncomprehending or too vulnerable to provide such community consultation.

Guideline: If in the view of the IRB, there is a reasonable probability that a prospective subject population would not consent to undisclosed purpose research if the purpose were disclosed in advance, the IRB should develop a suitable mechanism for obtaining surrogate consent.

Unseen observer research

As noted earlier (3, at pp. 77-79) in some sorts of research it would defeat the purpose of the research if the subjects were aware that the research was being conducted. It was further pointed out that unseen observer research is not limited to the social sciences. In certain cases the purposes of unseen observer research would be defeated by making the subjects aware of the research.

Guideline: If in the view of the IRB, there is a reasonable probability that a prospective subject population would not consent to unseen observer research if they were made aware of the fact of its existence, the IRB should develop a suitable mechanism for obtaining surrogate consent.

Conflicts of interest

In many cases there may be conflicts between individuals or groups having legitimate interests as to whether research should be conducted. The conflicts may be between society in general on one hand, and on the other, groups of individuals who might be perceived as enemies of society. These sorts of conflicts are not limited to social research. Thus, for example, in studies of the pathogenesis, prevalence, or incidence of occupational diseases there are

often conflicts between management and labor as to whether the research should be done. Perhaps the Commission will wish to develop guidelines as to how such conflicts might be resolved.

There is much controversy as to whether the results of research that has been conducted unethically should be published (9, at p. 58-59). Opposing points of view have been developed in detail by Levine (12) and DeBakey (13). Such considerations are beyond the scope of this paper. However, Makarushka (14) has suggested that even when research is done with informed consent--and, in all other respects is conducted ethically--there may be some unexpected findings that are so harmful to a group that they should not be published. I share the author's pessimism that this view can be translated into a guideline.

INCAPABLE SUBJECTS

Incapable is defined as an adjective (15): "1) Lacking capacity, ability or qualification for the purpose or end in view". To develop more fully the meaning intended of this word, incapable persons are identified as those not meeting the definition of the adjective, capable: "4: Having sufficient power, prowess, intelligence, resources, strength, or other needed attributes to perform or accomplish".

Thus, incapable subjects will be defined as those lacking sufficient power, prowess, intelligence, or resources to either perform or accomplish: a) participation in the research, or b) the protection of their own rights and welfare.

Those persons who might be incapable of participation in research by virtue of lacking the necessary biological or social attributes have been

discussed earlier. It should also be noted that--particularly when cooperation on the part of the subject is required--some individuals having the necessary attributes to test the hypothesis may be too uncomprehending or feeble to do what is expected of them. The primary focus of this section is to discuss the problems associated with selection of research subjects who are incapable of protection of their own rights and welfare. These individuals will be further classified as follows: 1) Uncomprehending; 2) Vulnerable; and 3) Dependent.

It should be understood that each of us when measured against the highest standards of capability will be found relatively uncomprehending, vulnerable, or dependent upon someone or something. Each of these categories should be viewed as consisting of a spectrum ranging from slightly to absolutely incapable. The following discussion will be concerned only with those sorts of individuals whose capabilities might be reduced to the extent that we might wish to treat them differently from most other individuals as we are considering the selection of research subjects. Also, in each category it will be recognized that incapacities may be transient, prolonged, permanent, or recurrent. These factors will influence the assessment of each incapability as it relates to the selection of subjects.

1) Uncomprehending subjects

Some barriers to comprehension were discussed earlier (3, at pp. 31-33); some devices that might be used to overcome some of these barriers have also been discussed. Among the problems that may be presented by inclusion of the uncomprehending as research subjects are: Consent may be invalid by virtue of this incapacity. In research activities requiring cooperation, the subjects may

not understand how they are to cooperate and, thus, either defeat the purposes of the study or contribute to their own harm.

Persons having prolonged or, perhaps, permanent incapacity to comprehend include the mentally retarded, the uneducated, and the senile. Language barriers may sometimes be overcome with the aid of translators.

Persons with various psychological disturbances may be incapable of comprehension transiently, for prolonged periods, permanently or intermittently. In some persons this incapacity may be absolute. Some very withdrawn schizophrenics might comprehend but give no evidence that they have. Some intelligent individuals, during obsessional states, may be so preoccupied with their obsessions that they have no energy or interest available to comprehend anything else.

Persons who are inebriated may have incapacities to comprehend ranging from barely perceptible to absolute. In some cases the inebriated person may insist that he is better able to comprehend than another person has told him he is. Inebriation is ordinarily intermittent. Most often, a person who can reasonably assume that he will be inebriated at some future time is capable of comprehending plans to involve him in research during his inebriation. It may be, for example, that his inebriation will be induced by administration of some drug for therapeutic purposes; eg, a narcotic, barbiturate, and so on. Under some circumstances it might be appropriate for a person to consent in anticipation of inebriation to being treated in a certain way when he is inebriated even though while inebriated he might object to being treated in that way.

Unconscious persons are absolutely uncomprehending. Unconsciousness may be intermittent and reasonably predictable as in individuals with grand mal epilepsy. Such individuals are ordinarily capable of valid consent in anticipation of their next unconscious period. Similarly, a plan may be developed between a physician and a patient to produce unconsciousness--eg, through general anesthesia--at some future time. This individual can consent in advance to various research procedures that might be done during the period of unconsciousness.

In summary, the uncomprehending subject is classified as incapable largely by virtue of being unable to comprehend the information necessary to provide valid consent. The following are general formulations for the development of guidelines for the selection of uncomprehending subjects.

a) In those who are intermittently or predictably inebriated or unconscious, consent can usually be negotiated in advance. If there is some cause to suspect that one's judgment might change while inebriated, it should be negotiated in advance whether the change in judgment is to be honored. More specifically, the person who expects to become inebriated may consent to have his judgment while not inebriated take priority over any expressions to the contrary while inebriated.

b) In developing guidelines to participate in research that presents mere inconvenience as opposed to risk of physical or psychological harm, standards for comprehension should not be set too high. If they are, it will tend to exclude inappropriately some persons from assuming the role of subject as a job. In general, it should be assumed that a person is capable of suitable comprehension unless this is demonstrably not the case. When in

doubt, comprehension can be assured with the aid of third party scrutiny (3, at pp. 46-52) or the 2-part consent form (3, at p. 33).

c) In developing guidelines to participate in research that presents known and/or unknown risk of physical or psychological harm, standards for comprehension should be set rather high. To the extent that the benefits of such research will accrue more to the class of persons represented by the subject than directly to the uncomprehending subject there should be an increasing presumption of the necessity for third party scrutiny or the 2-part consent form.

d) In cases in which the intervention is categorized as innovative therapy and in which the physician-investigator and the IRB agree that this is as good as the best alternative therapy (innovative or otherwise) for a well-defined category of prospective subjects, if neither direct nor proxy consent is possible, consent may be presumed. In rare cases it may be appropriate to proceed without first having consulted the IRB (1, at pp. 17a-18a). However, in such situations the physician (or other health care professional) should be aware that subsequently he is likely to be held accountable for his actions to both the subject and the IRB.

e) The truly uncomprehending subject is, in general, not a suitable prospective subject for research unless the only individuals that possess the biologic attributes necessary to test the hypothesis are necessarily also uncomprehending. In such cases it will be necessary to have suitable proxy consent. In cases in which there might be difficult choices between reasonable alternatives and in cases in which there is known and/or unknown

risk assumed by individuals with a primary purpose of benefiting their class rather than with an expectation of direct health-related benefit, it may be appropriate to establish a mechanism for community consultation with proxies; this would serve to reduce the fragility of the individual proxy in negotiating informed consent with the investigator (cf, Dependent subjects). In some cases it might be appropriate to establish a mechanism for surrogate consultation. Thus, for example, a proposal to perform research on a group of uncomprehending schizophrenics might first be presented to a group of individuals who had once been uncomprehending schizophrenics. They might be asked if they would wish to have such research performed on them at a time when they were uncomprehending. The information obtained from such a group might be of value to the group assembled for purposes of community proxy consultation.

2) Vulnerable subjects

Vulnerable is defined as an adjective (15): "1: Capable of being wounded: Defenseless against injury". It should be quite clear that many of the individuals that have been classified as uncomprehending are also vulnerable by virtue of that incapacity. For example, who could be more vulnerable than the unconscious person? Similarly, many individuals who are vulnerable by virtue of being sick are also dependent.

Vulnerable individuals will be categorized further into two groups each deriving its vulnerability from different origins; these are: A) The sick; and B) the impoverished. A third category will be developed as the potentially vulnerable: C) Minorities.

A) The sick. The sick role and the barriers it presents to autonomy have

been discussed earlier (3, at pp. 34-39). A preliminary description of the relative vulnerability of various persons who are in the sick role has been presented earlier (2, at pp. 51-52). The definition of the sick role was written in a time when most definitions of diseases were prepared by physicians and most spokespersons for the public did not challenge these definitions. At that time all concerned were aware that some persons assumed the sick role more or less illegitimately. Those that did so most illegitimately were branded malingerers and those whose assumption of the sick role was controversial were branded hypochondriacs. Some individuals were assigned the designation sick against their wills; this mainly occurred in disputes over whether various sorts of personal behavior might be considered sickness as opposed to personal preference.

Now it is clear that over the past 20 years, society--sometimes with and at others without the collaboration or concurrence of health professionals--has begun to extend definitions of the sick role. Now we find that abusers of alcohol and various other drugs that affect cognitive function are assigned the sick role. Persons with various difficulties in learning how to read are treated as if they were sick. In some circumstances, voyeurism, prostitution, gambling, violence, and other such behaviors are considered sicknesses. A particular problem is presented when some of these behaviors that are seen as sicknesses are also seen as crimes. Thus, for example, a prostitute may be offered the "option" of either going to prison or enrolling in a "therapeutic" program.

One peculiarly anomalous situation is that of the homosexual in 1976. In some jurisdictions homosexual behavior is considered criminal. Recently,

the American Psychiatric Association voted that homosexuality was not an illness. Thus one wonders whether a homosexual can be offered the "option" of enrollment in a therapeutic program as an alternative to imprisonment. Also, one wonders whether a homosexual who perceives his own homosexuality as an illness of which he would rather be rid can appeal to a psychiatrist or a psychologist for therapy.

For the present purposes, sickness will be defined as a state as perceived and defined by the individual assuming the sick role. Further, it will be defined as a state which the individual would abandon--with the aid of technically competent help--in favor of a condition that he would perceive as healthy or at least more healthy than he is.

Persons with short term illnesses from which they might be expected to recover completely without the aid of health professionals will not be considered vulnerable. Persons with illnesses from which they might be able to recover completely but only with the aid of standard (non-experimental) technically competent help will not be considered particularly vulnerable; this statement is based on the assumption that such help will never be withheld as punishment for refusal to become a research subject.

Persons having prolonged chronic illnesses which are refractory to standard therapeutic modalities may be seen as seriously vulnerable. This becomes increasingly true when such people perceive themselves as "desperate" and willing to take "any risk" for even a remote possibility of relief. In this category are some infertile persons or couples who "desperately" want a child; some persons with chronic, painful, and disabling disorders such as rheumatoid arthritis; some obese persons who cannot lose weight following

standard procedures; some persons with severe depression, obsessive-compulsive disorders; and so on. Depressed persons and others who question their self-worth may be especially vulnerable to inappropriate inducement by offering benefits other than those directly related to their health (2, at pp. 39-41).

Perhaps the most vulnerable group among those who have assumed the sick role are some persons who believe (correctly or incorrectly) that their own death is imminent. This will be an especially difficult group for which to develop guidelines.

It has been proposed by Gaylin (16) that a new class of subject called the "neomort" might be developed. A neomort is an individual who has been declared dead by virtue of current criteria for establishing brain death whose other bodily functions are maintained more or less indefinitely with the aid of various devices. He suggests that we now tolerate such activity to a limited extent. Persons who have been declared dead by brain death criteria and who are to be donors of an organ now have their biologic functions maintained by perfusion of various fluids and nutrients and with the aid of "life-sustaining" devices until the transplant recipient is prepared to receive the organ. A person might volunteer for neomort status in much the same way as one now consents to posthumous donation of an organ under the Uniform Anatomical Gift Act. Presuming their lack of sentience, these persons might be maintained indefinitely for a variety of biological research procedures that for various reasons one might not wish to perform on sentient beings. Additionally, organs and tissues might be harvested as necessary for transplant purposes.

I shall not comment further on neomorts; perhaps the Commission will wish to develop guidelines in this regard.

General considerations for the development of guidelines to protect subjects who are vulnerable by virtue of being sick:

a) Persons having prolonged chronic illnesses which are refractory to standard therapeutic modalities are particularly vulnerable to taking risks for even remote possibilities of relief when they perceive themselves as "desperate". In the past, such persons were particularly vulnerable to exploitation by individuals offering "miracle-cures" such as copper bracelets, rainbow pills, Krebiozin, and so on. Such persons are most likely to be protected by requirements that all innovative therapies are to be: "conducted according to the highest standards of the relevant scientific discipline (1, at p. 16a)." This presumes that they will first be reviewed by an IRB which will have sufficient expertise to review the proposed innovative therapy for scientific merit.

b) Persons who question their self-worth may be especially vulnerable to inappropriate inducement by offering benefits other than those directly related to their health. Thus, it seems appropriate that the guidelines reflect a need for caution not to exploit such persons. On the other hand, advice given to those responsible for selection of subjects should not be too rigid. Some persons by virtue of being excluded might have their senses of self-esteem diminished further.

c) The most difficult group with which to deal will be those who perceive themselves as dying. Some of these persons are particularly susceptible to loneliness; inappropriate exclusion of such persons from "normal human activities" might intensify their feelings of loneliness. Thus, it would be clearly

inappropriate to develop rigid guidelines excluding dying persons from research characterized by mere inconvenience.

On the other hand, it is frequently alleged that in the past, dying subjects were commonly exposed to high risk research not conducted for their benefit because it was impossible to cause any lasting harm. Examples of exposure of dying persons to high risk research not done for their benefit have been assembled by Katz (17, at pp. 1054-1062).

In general, research on dying persons which presents known and/or unknown risk should be limited to that in which the dying person--or at least that class of persons which he represents--is likely to receive direct health-related benefits. Experiments designed to use the dying person merely because there is no further way of causing him damage--particularly when these are done without meticulous negotiations for informed consent--are an affront to the dignity of such persons. It is my undocumented view that such experimentation is now rare. On the other hand, Spiro has presented the equally undocumented view (18) that the person with cancer is often viewed as dehumanized, "and too often studies that would not be done on the healthy are projected for him simply because he is going to die sooner than the rest."

On the other hand, guidelines should not be so rigid as to proscribe altruistic acts done with meticulously negotiated informed consent such as donation of an organ or tissue according to the provisions of the Uniform Anatomical Gift Act.

d) Those who are vulnerable by virtue of having assumed the sick role are, in general, the most suitable subjects for most biomedical research. That is, they have the biological attributes necessary to test the hypotheses of most

biomedical research. To the extent that the research is done with the intent of bringing direct health related benefit to the subject this seems to present little problem; exceptions may be seen in cases in which sick persons might have dependent relationships jeopardized (cf, Dependent subjects).

A greater problem is presented when sick persons are asked to assume known risk with the expectation that the benefits will redound more to the class of persons whom they represent than to themselves. In estimating the potential benefits of research to a class of persons, the investigator is likely to err, if at all, on the side of overestimating. The individual sick person tends not to be strategically placed either to disagree with the investigator's estimate or to refuse an appeal to do good for others. Thus, it will be proposed that in research presenting known risk or in some categories of research presenting unknown risk (where there is some cause to presume that the unknown risk might be substantial) and the purpose of the research is to develop information that is more likely to benefit the class than the individual, community consultation is required. The class of persons who will receive the benefits is better situated than either the investigator or the individual prospective subject to decide whether the benefits are sufficiently great that they would wish to expose even a small number of their class to the known or unknown risks. In addition, at a meeting of prospective subjects the fragility of the individual should be reduced. In some cases it may be appropriate to establish lottery systems to determine who will be the subjects of such research (cf, Lottery systems).

In some cases the proposed subject population may be so fragile that surrogate consultation may be required (cf, Known risks--2).

e) In some cases there will be competition for scarce innovative therapies; it will be proposed that the most fair way to determine who shall be the recipients among those having equal medical needs will be a lottery.

f) Commonly, those who are vulnerable by virtue of having assumed the sick role are also dependent upon either an institution or a professional. Thus, some additional problems in selection of vulnerable subjects are discussed in detail in the section on dependent subjects.

B) The impoverished: To the extent that a person lacks the funds to purchase what he considers the necessities of existence, his freedom to refuse to consent to do anything that might improve his purchasing power may be limited. Within a population sharing comparable incomes various individuals may assign different priorities to television sets, food, heat, clothing, and so on. Some persons with what appear to be relatively high incomes do extraordinary things to earn sufficient money to purchase what they consider the necessities of existence; eg, a third family automobile or membership in a country club. It is not the purpose of this paper to analyze the responsibility of individuals to budget their resources appropriately. However, it may be recalled that some regulations and policies on disbursement of public funds for health or welfare seem to be developed to prevent what policy-makers perceive as irresponsible budgeting; eg, funds may be provided as food-stamps which are not legitimately negotiable for anything other than food. Similarly, to become eligible for some types of publicly funded health care one must dis-

pose of any real property above a specified level.

For purposes of identifying a class of people who might be considered vulnerable by virtue of economic impoverishment, impoverishment is defined as a condition in which a person considers it necessary to take extraordinary risks to secure money or other economic benefits that will enable him to purchase what he considers to be the necessities of life. Further, his willingness to take extraordinary risks is based upon his belief that he cannot secure a sufficient amount of money by ordinary means. This category intersects but is not identical with that of dependent by virtue of being on welfare.

The Commission may wish to consider the following guideline to protect the impoverished: Economic inducements to participate in research should be determined by the amount of inconvenience to be imposed on the subject and should not be based on calculations of known or unknown risk. As a corollary to this guideline it might be stated that research subjects should not be paid to assume risk; they should rather be compensated for injury.

This guideline, if adopted, would represent a departure from the tradition in our society that persons are commonly paid high salaries to assume large risks. Therefore, in order to justify adoption of this guideline it will be necessary to provide justification for this departure from tradition.

It is customary to conduct most research activities without cost to the subject. At times, an impoverished person may find himself faced with the necessity to assume a large financial burden to purchase needed medical care for himself or for a dependent. He may find that if he or his dependent is a suitable prospective subject for research, the costs of the needed medical care may be largely underwritten by the agency sponsoring the research. Thus,

the "choice" between being a patient or a subject may be based primarily on financial considerations. I doubt that this dilemma can be entirely resolved through the development of guidelines. In particular, when choosing between an innovative therapy and a customary medical procedure, if the innovative therapy is provided free, some persons will choose the innovation largely on that basis. A guideline might be developed that would require the subject to finance innovative therapy much in the same way the patient finances medical care. This seems inappropriate to me; particularly, in the early stages of testing the innovative therapy--when the risks and potential benefits are largely unknown and when the testing is done for the benefit not only of the subject but also of like persons--it seems inappropriate to call upon the subject to assume not only the direct health related risks but also the financial burdens.

It may be possible to minimize the possibility of some undue economic inducement through the development of a guideline. This guideline would not resolve the issues of choice between innovative therapies and customary medical practice. It assumes that it is appropriate to provide economic inducement to assume inconvenience.

General formulation of a guideline: In calculating the costs of health services to an individual who will simultaneously play the roles of subject and patient, it should be calculated how much his medical care would have cost had he not agreed to play the role of subject. This amount should be paid by the patient. The additional costs incurred as a consequence of agreement to play the role of subject should be paid by the investigator or sponsoring agency.

C) Minority groups. Individuals who are members of minority groups (as determined by race, sex, ethnicity, and so on) are not to be considered particularly vulnerable a priori. Because the group may be the object of discriminatory societal customs, an inordinantly high percentage of the group may be classified as uncomprehending, vulnerable, or dependent by virtue of other criteria. Such persons should be treated accordingly.

The interests of members of minority groups are probably best protected by representation on the IRB.

3) Dependent subjects

Dependent is defined as an adjective (15): "2b: Unable to exist, sustain oneself, or act suitably or normally without the assistance or direction of another or others." "c: Connected in a subordinate relationship...d: Lacking the necessary means of support and receiving aid from others".

Most persons are dependent upon some other persons or institutions for most of their lives. For purposes of this discussion we shall focus on dependent relationships that present either of two potentials. The first is that by virtue of the relationship, the dependent individual is administratively more available to the researcher to be selected as a subject than are other individuals not having the same dependent status. The second is that in which the dependent individual might fear that he might forfeit either in part or in whole his dependent status by virtue of refusing to become a subject.

The institutions upon which an individual might become dependent and which present these two potential problems include health delivery systems, educational institutions, welfare agencies, places of employment, and so on.

Within such institutions the problems become more serious when the individuals have no reasonable alternatives. For example, a person who is dependent for his health care on Veterans Administration Hospitals will be viewed as more dependent than one who has his choice between several private hospitals in the same city. Clearly, it is common that individuals develop more intense dependent relationships with certain individuals within these institutions. Thus, for example, Spiro (18) suggests that a physician having a close relationship with a patient can ordinarily persuade that patient to consent to nearly anything.

The author accepts the notion that dependent persons are particularly liable to feel that their dependent relationships may be jeopardized if they refuse to consent to become research subjects (2, at pp. 14-15); this is particularly true when the professional with whom they are negotiating informed consent is the one with whom they have established an intense dependent relationship and when that professional has a vested interest in having the individual assume the role of subject. Recent discussions by the Commission suggest that many of them share this assumption. For example, in discussions of prisoners and patients as prospective research subjects there is often reference to the "fragility of the individual" who is either vulnerable (by virtue of having assumed the sick role) or dependent in negotiating with the more powerful professional. The previously described process of community consultation may be used to reduce the fragility of the prospective dependent research subject in relation to the investigator (cf, Lottery systems).

General considerations for the development of guidelines for the selection of dependent subjects:

In general, it is appropriate to draw upon the administratively available to assume inconvenience. However, in research presenting risk of physical or psychological harm, as the degree of risk increases there should be a decreasing assumption of the validity of drawing upon the administratively available. In situations in which known risk is presented in order to develop basic information that will be of presumed benefit to the class represented by the administratively available, there should be a decreasing assumption of the appropriateness of drawing upon the administratively available without consulting them as a group. Thus, in some cases it will be necessary to seek community consultation (cf, Lottery systems) and in others, community consent (cf, Randomized clinical trial).

In general, it is not appropriate to threaten individuals with loss of dependent status owing to unwillingness to assume known and/or unknown risks of physical or psychological harm. Some rare exceptions to this generality will be stated. For example, there are some cases in which research presenting known and/or unknown risk is necessary to establish a category of employment; in such cases it may be appropriate to offer such employment contingent upon an individual's willingness to be a subject of such research (cf, Research presenting unknown risk of physical or psychological harm--2).

Most innovative therapies are viewed as presenting either unknown or combinations of known and unknown risk of physical or psychological harm. In general, it is assumed that most persons can choose to receive an innovative therapy. However, the choice to receive an innovative therapy imposes upon the individual the reciprocal obligation of assuming the inconvenience of tests

necessary to prove its safety and/or efficacy. In cases in which the innovative therapy is scarce, refusal to participate in tests necessary to prove its safety and/or efficacy may justify exclusion of that individual; examples of such research have been presented earlier (3, at pp. 28-30). However, a distinction must be made between depriving a person of a single modality (innovative therapy) on the one hand and, on the other, of an entire dependent relationship. It is not appropriate to terminate a professional-client relationship because the client refuses to be the subject of research--including innovative therapy.

Categories of dependent persons that will not be discussed further here are children and prisoners. There will be some additional discussion of children in the section entitled research presenting combinations of known and unknown risk of physical or psychological harm--2. However, in general, children and prisoners cannot be considered as can the sorts of dependent persons discussed in this paper. The issues involved are entirely different in kind.

COMPENSATION

In an earlier paper (2, at pp. 27-29), mention was made of the need to develop adequate plans for compensation of subjects who are harmed by research. Attention was further called to the Secretary's (DHEW) Task Force on the Compensation of Injured Research Subjects along with a suggestion that the Commission might wish to establish formal communications with this group. Several approaches to insuring research subjects were also reviewed. It is the opinion of the author that it will be most difficult to develop appropriate guidelines

for the selection of subjects for research having either unknown or known risk of physical or psychological harm without first having made plans for adequate compensation of those who are harmed. Subsequently stated guidelines are based on the assumption that appropriate mechanisms for compensation of harmed subjects will be developed.

A recent article by Adams and Shea-Stonum reviews the various approaches that might be used to compensate harmed subjects (19). This article calls attention to the fact that early drafts of the legislation leading to PL 93-348 would have charged the Commission with the task of developing "a mechanism for the compensation of individuals and their families for injuries or death proximately caused by participation of such individual in a biomedical or behavioral program." However, as the tenure of the Commission was reduced from five to two years and the authority from regulatory to advisory, the language of this charge to the Commission evolved accordingly. Thus, the Commission is charged to "make recommendations to the secretary...concerning any other matter (in addition to administrative procedures necessary to implement ethical guidelines in conducting research) pertaining to the protection of human subjects of biomedical and behavioral research.". Thus it appears, that the legislative intent was that the Commission might examine the issue of compensation and make recommendations accordingly.

Adams and Shea-Stonum identify three types of situations in which subjects might be injured (19, at pp. 614-616):

"First, the common negligence of the researcher-physician may cause injury to the volunteer. Secondly, injury may arise in an experiment that should not have been conducted in the first place. Experiments that failed to meet the prevailing standards for approving the use of human volunteers or that lack ade-

quate consent of the subject fall within the second category. In such situations the injury complained of may or may not be related to a defect in the execution of the experiment. Finally, injury to the volunteer may occur notwithstanding the absence of negligence, the appropriate approval of the experiment, and the subject's valid consent. Such unavoidable injuries are the specific untoward results that have given society pause in accepting human experimentation."

In the first two types of situations there are available appropriate common law remedies; ie, actions for malpractice. It is the third type of situation that requires a new development.

It seems clear (19, at p. 623) that in the medical practice context, the patient assumes the risk of any harm to which he has consented. "In the experimental situation, however, the unknown risk is the greatest source of potential injury. Consequently, a subject who consents to experimentation with the specific knowledge that injury may result from an unknown risk and who suffers harm from such a cause would not be afforded a remedy under the present common law concept of consent."

After reviewing various legal approaches to providing economic remedies for harmed research subjects, the authors conclude that the most appropriate might be to develop a type of compensation fund. This fund would be established and maintained by the federal government for all research including that not sponsored by the federal government. In theory it is developed as a modified workmen's compensation plan. Like workmen's compensation, subject's compensation would be largely a no-fault system. Unlike workmen's compensation, there would be the possibility of resorting to common law remedies if the investigator or sponsoring agency were at fault. In particular, if the investigator proceeded negligently or if the research were done without appropriate IRB sanction, either the harmed subject or the compensation fund could proceed against the investigator or sponsoring agency.

The premise on which this latter proposal is based is contained in the following paragraph (19, at p. 639):

"In the field of medical experimentation, fault is not the two-sided coin

that it is in industrial accidents. Injuries will rarely, if ever, result from the subject's negligence or fault. Therefore, the reasons for limiting coverage in workmen's compensation to injuries affecting the ability to work and for denying recovery for pain and suffering are not operative in the researcher-subject relationship. Furthermore, since subject fault is not an issue, the researchers have no basis for demanding that their fault also be ignored. In making reference to the workmen's compensation model, we must not lose sight of the policy and politics that caused it to preempt the control system of the common law."

Although I must disagree with the premises for this argument--there are many ways in which subjects might contribute to their own harm (eg, at pp. 16-17)--I must agree with the conclusion that harmed subjects might seek common law remedies for harm occurring as a consequence of investigator negligence.

This proposal also includes a system of indemnification of the compensation fund by the sponsor of the research which is based upon calculations of the probability and magnitude of both harm and benefit and also considerations of whether the benefits are expected to be enjoyed by individual subjects or by others. It is proposed that this system--particularly the component having to do with judgments of the amount of indemnification--would yield salutary effects to the entire process of determining the appropriateness of any particular research proposal. It would at least clarify the costs of conducting any particular proposal in economic terms. In my view, it would also facilitate the development of appropriate guidelines for selection of subjects.

I do not think the system offered in this article is ideal. However, it does provide a point of departure for considering a suitable system as well as a good account of the advantages that might be afforded by one. One problem that is not addressed is that most workmen's compensation funds are

based on the premise that all persons who might be compensated hold jobs for which they receive predictable amounts of income in the institution in which they might be harmed. Thus, for example, it is relatively easy to calculate how much income is lost by the workman who is incapacitated for 2 months from performing a job that yields a salary of \$4.00 per hour. In order to apply the concepts of workmen's compensation to compensation for harmed subjects, it must be determined whether the compensation would be relative to the subject's expectations in other jobs he might hold. Thus, it might be determined that the individual whose only income is welfare might be entitled to no compensation for prolonged disability. This would appear to be a peak achievement in inequitable compensation. On the other hand, a system that provided equal compensation for all subjects harmed in a similar fashion would cause society to impose known and unknown risks largely on the economically disadvantaged.

I should also like to take exception to the notion that the compensation fund must be established and maintained by the federal government. It would be more appropriate to have compensation funds developed as they now are for workmen's compensation by various employers and sponsors in accord with appropriate state and federal regulation. I see no cause to distribute the "costs" of research uniformly throughout society unless the profits will be similarly distributed.

LOTTERY SYSTEMS

In recent years there have been several proposals that it might be most appropriate to select subjects for certain types of research according to lottery systems. Some authors have focused on the problem of distributing

the risks of research in accord with principles of justice as fairness (11). Thus, Fried (10, at p. 64 et seq), in discussing the special case of research called the randomized clinical trial (RCT) accepts the notion that in innovative therapy the appropriate prospective subject population is developed according to a natural lottery. He then proceeds to argue against those who say it is appropriate to determine who among the prospective subject population will receive which treatment (of two or more that are to be compared) according to a lottery. I must agree with his argument. The real problem is to determine fair systems for selection of subjects among whom competing modes of therapy will be tested.

Capron (20, at p. 147), in discussing another special case--drug trials in children--has suggested that a lottery might be used to determine who will be the subjects of research. Having accepted the need for phase I drug testing in children, he suggests:

"If we are, in fact, speaking of a definable group and if all members of the group have a roughly equal chance of being afflicted with the diseases which are to be treated in the group, then consideration should be given to selecting experimental subjects from the group on a random basis."

The system suggested by Capron is rather like the selective service system; it is proposed as a system that would obviate the requirement for informed consent.

Others have focused on the utility of lottery systems to assure equal access on the part of all persons to therapies (innovative and otherwise) for which demand exceeds supply. Thus, for example, the Artificial Heart Assessment Panel of the National Heart and Lung Institute (21, at pp. 197-198) concludes:

"(5) In the event artificial heart resources are in scarce supply, decisions as to the selection of candidates for implantation of the artificial heart should be made by physicians and medical institutions on the basis of medical criteria. If the pool of patients with equal medical needs exceeds supply, procedures should be devised for some form of random selection. Social worth criteria should not be used, and every effort should be exerted to minimize the possibility that social worth may implicitly be taken into account."

Outka (22) has analyzed in detail the issues of equal access to health care in relation to principles of social justice. He concludes most strongly that considerations of merit, desert, societal contribution, and so on, have no place in making decisions on the allocation of the goods of health care. The most important principle he develops is: "To each according to his essential needs." Essential needs are distinguished from desires or wants. Essential needs in this case are illnesses or disabilities defined by medical criteria and distributed according to a natural lottery. Outka acknowledges that in many cases the deliberate acts of individuals or institutions may contribute to the development of various diseases; however, he illustrates quite graphically how complex decision-making might become if we attempt to depart from the natural lottery model. A second principle that he finds useful in decision-making is: "Similar treatment for similar cases." However, this second principle is not germane to the selection of subjects for established categories of research. Rather, it is employed to determine which categories of research (or innovative therapy) to establish. He uses it principally to establish categories of individuals for whom therapy will not be developed.

Thus, Outka agrees with Ramsey (23, at p. 252 et seq) that when one must decide between claimants for a medical treatment unavailable to all, it might be most appropriate to develop a policy of random patient selection. He further agrees that the best suitable alternative might be to deny all persons in certain

categories specific medical treatment.

I should now like to propose a general approach to developing lottery systems for recruiting subjects for research characterized as having either known or unknown risk of physical or psychological harm. This approach has built into it a device for securing community consultation to determine whether the group as a group perceives the potential benefits of the research as being sufficient to merit the presentation of the risk to even a small number of them. Further, entry into the lottery may be validated only by the informed consent of the individual.

It would be most appropriate to use this form of lottery in the very early stages of innovative therapy where there is some cause to suspect that there might be substantial risk. Thus, for example, it might be used to determine the first persons upon whom an invasive diagnostic technique-- eg, needle biopsy of the kidney, cardiac catheterization, and so on--is tried. It would also be appropriate to use this system in research in which a subject assumes known risk for purposes of developing biological information about a class of persons with no immediate prospect of direct personal health-related benefit. Although the primary purpose of developing lottery systems is to achieve fair distribution of risk, other advantages of this proposal will be specified.

Procedures

1) A formal description should be prepared of the biological attributes the prospective subjects must have in order to test the hypothesis.

2) The proposal to conduct the research--including the formal description of prospective subjects--should be disseminated widely through the community

upon which it is planned to draw for prospective subjects. This might be accomplished through advertisement. It is now common practice to advertise to recruit subjects for basic research. However, recruiting subjects for innovative therapy may be seen as conflicting with ethical codes of medical societies proscribing advertisement of physicians' services. Parenthetically, at the time of this writing the Federal Trade Commission is considering development of regulations that would require physicians to advertise (24). Alternatively, the research proposal might be circulated among practicing physicians along with a request that they inform those of their patients having the needed biological attributes of the proposal. This procedure is now commonly utilized by the National Institutes of Health (NIH). They commonly circulate letters to practicing physicians to recruit subjects with various disorders. An additional mechanism might involve publication of announcements of the proposed research in medical journals.

One purpose of such wide dissemination of the proposal is to minimize the probability of exploitation of the administratively available. Another purpose is to get the broadest possible base of opinion to serve the objectives of community consultation.

3) The individuals having the necessary biological attributes should be informed that there will be a meeting at which the research proposal will be discussed. They should further be informed that the first purpose of the meeting is to determine whether the research should be conducted. Further, they should be informed that they will not be called upon to serve as subjects without their informed consent; ie, attendance at the meeting does not commit one to serving as a subject should it be decided to proceed with the research.

Those who are interested should be requested to contact the individual who will convene the meeting (ordinarily the investigator).

4) When a sufficient number of prospective subjects have indicated their interest, the meeting should be convened. At this meeting the investigator(s) should communicate to the assembled prospective subjects all relevant details of the proposal. The purposes of this assembly include those of community consultation. It would most effectively accomplish one of the previously specified functions of informed consent; ie, "To involve the public" (3, at p. 3).

At this meeting the fragility of the individual in relation to the investigator should be reduced considerably. The prospective subjects will greatly outnumber the investigators. One might expect that they would develop a sense of community. They may, for example, decide that the collective benefit is insufficient to merit the degree of risk to be borne by even a small number of them. Through the development of this sense of community, the prospective subject population may develop a sense of cohesiveness and mutual support. One of the effects of this might be to mitigate--to some extent--against some of the hazards of depending upon the volunteer mechanism that have been detailed earlier as some types of derivative psychological risks (2, at pp. 10-15).

The group should be informed that subjects for the research will be chosen by a lottery and that no person will participate in the lottery without having first consented as an individual.

4) An attempt should be made to have at least 5-10 times as many persons volunteer for participation in the lottery than will actually be

used as subjects. If the group has determined by majority vote that it is appropriate to proceed with the research yet only a tiny minority of the group volunteers for participation in the lottery, one might suspect the validity of the process for that particular proposal. The credibility of the lottery system would certainly be enhanced if those investigators having the biologic attributes needed for participation volunteered for the lottery.

5) In the case of innovative therapy all persons who consent to become part of the lottery would be promised first access to the innovation should it prove to be suitably safe and effective. The offer of first access as an "inducement" to participate in therapeutic innovation is not without precedent; eg, in the initial placebo-controlled trials of polio vaccine, such an offer was made to the families of the children whose parents consented to their participation (10, at p. 147).

CATEGORIES OF RESEARCH REEXAMINED

Research presenting mere inconvenience to the subject--2

Guidelines: In research presenting mere inconvenience--but neither known or unknown risks of physical or psychological harm--all humans may be considered appropriate subjects providing that:

a) The subjects have sufficient capacity to comprehend not only to give suitable consent to become a subject but also to perform the duties expected of a subject. Truly uncomprehending subjects should be used only if no other class of humans possesses the needed biological attributes to test the hypothesis

of the research; in such cases, proxy consent is required.

b) Refusal to become a subject will not jeopardize a dependent relationship desired by the subject; exceptions may be justified by community consent of those sharing the dependent relationship. In general, these exceptions should be allowed only when the proposed research is clearly in the interests of improving the institution.

There are some features of this guideline that may be perceived by some as disadvantageous. To the extent that economic inducements are offered to participate in this type of research, there will tend to be a disproportionately high representation in the subject population of those who are on welfare and others who perceive themselves as impoverished. To the extent that psychosocial benefits are offered--explicitly--^{or implicitly} there will tend to be a disproportionately high representation of the "administratively available" and those who question their own self-worth. (I doubt that guidelines can be developed to resolve the latter problem. However, investigators could be reminded to avoid inappropriate capitalization on the vulnerabilities of such persons.)

Research presenting unknown risk of physical or psychological harm--2

Guideline: In research activities entailing unknown risk all reasonable effort should be made to conjoin the direct health interests of the subjects to the ends of the research. This guideline is most easily applicable in conducting activities that have been defined previously as innovative: therapy (1, at 9a-18a).

If this guideline is adopted it would change drastically the ways in which new drugs are developed in the United States. It would be tantamount

to saying that most phase I drug testing is inappropriate. It would not particularly change the approach to research in any other category of innovative therapy. For example, we do not now find it necessary to prove that innovative approaches to surgery, invasive diagnostic techniques (including biopsies and catheterizations), diagnostic and therapeutic devices, use of radioisotopes, radiation and other physical forms of therapy, and behavioral approaches to psychotherapy are safe in "normal humans" before we proceed to determine whether they are effective in the populations they are intended to benefit.

The disadvantages of Phase I testing of new drugs were explored in detail at a recent conference (25). To summarize some of the arguments:

Azarnoff (25, at p. 796 et seq) concluded: "The wisdom of routine testing of drugs in healthy volunteers is questioned on two counts: Scientific validity and the dubious ethical practice of giving normal individuals drugs that are not for their benefit and may be harmful to them. The metabolism of drugs is so changed by numerous diseases that any transfer of results from healthy volunteers to patients may be dangerously misleading. Drug interactions also modify results and must be evaluated in both normal and patient-subjects."

Oates (25, at p. 809 et seq) concluded: "The determination of safety and adverse effects in Phase I together with investigations on the disposition and bioavailability of the drug often provide a better scientific and ethical basis if conducted with knowledge of the dose required to produce the desired pharmacologic effect. Because certain pharmacologic effects are specific for the disease state, Phase I studies on such drugs should be conducted only in carefully selected patients with the appropriate disease."

Hollister (25, at p. 803 et seq), in discussing problems peculiar to early studies on psychotherapeutic drugs emphasized: "It does not seem likely that one can predict these (psychotherapeutic) effects in any useful or innovative way from the study of such drugs in normal, asymptomatic human subjects."

There are some types of research that present unknown risk which are not designed to bring direct benefit to the subjects. In general, this type of research is designed to further our understanding of the biology of humans

or certain categories of humans (the categories may be determined in a variety of ways including the possession of a certain disease). At times it is hoped that based upon improved understandings of the biology of humans it will be possible to develop an innovative approach to therapy. However, almost all techniques used to develop improved understandings of biology in persons with various diseases have known risks and should be treated accordingly.

Let us now consider research procedures having truly unknown risks which are not designed to bring direct health benefit to particular subjects. In general, it should be possible to identify prospective subject populations whose interests most closely approximate those of the research. Alternatively, it should be possible to identify individuals who experience similar conditions as will be created for research purposes in the course of their usual activities. Thus, for example, the first experiments designed to test the effects of high barometric pressure might most appropriately be done on individuals who experience such conditions routinely; eg, deep sea divers. Research designed to determine the physiological effects of prolonged exposure to zero gravity first became of interest as the plans to develop the astronaut program were developing. Persons who were to become astronauts would experience zero gravity conditions for prolonged periods. It would have been impossible to develop the astronaut program without knowing the effects of zero gravity, whether it could be tolerated, and what measures could be taken to offset potentially harmful effects--if any. Thus, it seems that it might be most appropriate to select as the initial subjects for such studies those who wished to become astronauts. It might be quite appropriate to inform those who wish to become astronauts that they will not be accepted unless they are

willing to assume the unknown risk of research designed to test the physiological effects of zero gravity. This suggests the exclusion stated earlier to the general formulation for guidelines for the selection of dependent subjects; viz, there are some rare cases in which research presenting known and/or unknown risk is necessary to establish a category of employment; in such cases it may be appropriate to offer such employment contingent upon an individual's willingness to be a subject of such research. Choices of who shall be the first, and so on, would be resolved most fairly through a lottery; in this case participation would not be voluntary.

Special cases of unknown risk research: In the course of medical practice, use of a "standard" prophylactic, diagnostic, or therapeutic modality may be associated with a severe adverse reaction. When this first occurs, there will almost always be uncertainty as to whether the modality was the cause of the reaction. Determinations as to whether the intervention and the reaction are causally related are necessary to enable one to predict with reasonable confidence the consequences of repeating that intervention in similar persons in the future. The traditional approaches to establishing correlations now most prevalent are as follows: a) The physician may write a "case report"; physicians who read the case report and who have seen similar correlations are thus prompted to report their own observations. b) In the event the adverse reaction is not potentially lethal or disabling, the individual who first experienced the adverse reaction and others like him may be exposed deliberately to the putative causative modality to see if the same adverse reaction recurs. c) Upon first observing an association between an intervention and an adverse reaction, a careful review may be made of the

consequences of performing this intervention in similar patients. This may be accomplished by review of medical records of similar patients.

Illustrative example: At one point it was first observed that the performance of an intravenous pyelogram (IVP) in a patient with multiple myeloma was followed by acute tubular necrosis (ATN). At the time it was known that ATN (an often severe and sometimes lethal kidney disease) was a very rare complication of IVP (a diagnostic test usually thought of as relatively harmless). Perhaps the first time this was observed, those who observed it did not think to draw a correlation. But at some point sufficient experience accumulated to permit formulation of the hypothesis as a question: Are persons with multiple myeloma peculiarly susceptible to this particular severe complication of this useful diagnostic test? At the point that accumulated experience indicates that it is legitimate to ask the question, it becomes necessary to categorize the use of this "standard" diagnostic procedure in persons with multiple myeloma as innovative therapy with unknown risk. All reasonable means to test the hypothesis without exposing new persons to serious risk should be exhausted before proceeding. Thus, for example, review of the medical records of persons with multiple myeloma may reveal a high incidence of ATN following IVP. However, for the sake of developing a guideline, let us suppose that the cause-effect relationship cannot be established without testing the IVP on additional persons with multiple myeloma.

Persons with multiple myeloma often develop kidney disease as a complication of their primary disease. However, they may also develop diseases of the kidney that are not related to their primary disease and which are

amenable to corrective therapy. The IVP may be most useful in distinguishing between the two types of disease. Other diagnostic tests may yield information similar to that obtainable with IVP. In order to get all of the information one can obtain from an IVP it is necessary to do several tests each of which present their own inconvenience and risks. Performance of some of these tests in individuals who are not peculiarly susceptible to ATN from IVPs carries with them significantly higher risk than does the IVP. However, the risk of all of these tests taken together and calculated as a function of probability plus magnitude of harm does not nearly equal the risk of say a 10 per cent probability of ATN. Thus, it is in the interest of the class of persons who have multiple myeloma to learn whether they are excessively susceptible to ATN following IVPs.

In this situation--and in like situations--it seems most appropriate to establish a modified form of lottery. In this case, a group of persons having multiple myeloma might be assembled. They should be informed of the probability that they might develop some sort of kidney disease and that at such time it will be in their interest to have appropriate diagnostic testing done. Then they might have presented to them the known and unknown risks and benefits of IVP as well as the known risks and benefits of alternative diagnostic techniques. They should be informed that at the time evidence of kidney disease develops in any of them, one or the other of the alternative approaches to diagnosis should be used. At this point--without knowing which among them might develop kidney disease and, of those, which might develop it first--they should be asked to choose between the alternatives. Some may choose to "play it relatively safe" assuming the relatively higher known risks of alternative diagnostic techniques. Those who choose for IVP will be further

chosen by the natural lottery. Those who choose for IVP should also agree in advance to have sophisticated tests done for the purpose of detecting mild or sub-clinical cases of ATN.

In this particular situation, it would be appropriate to disseminate widely the facts that the question had been raised and the research was being conducted. This would encourage other physician-investigators to either establish similar research procedures at their own medical centers or to refer appropriate patients to centers at which this research was being done. Even more importantly, it would caution physicians against imposing unknown risks inadvertently while awaiting the results of the research.

General formulation: The category of research presenting unknown risk of physical or psychological harm includes most activities classified as innovative therapy (practice) at the very earliest stages of their development. The most suitable subjects for such research are those who are vulnerable by virtue of having assumed the sick role. In general, subjects for this category of research should be the most capable available having the biological attributes necessary to test the hypothesis. In cases in which there is some a priori reason to predict serious harm--eg, as in the special case exemplified by testing IVPs in patients with multiple myeloma--community consultation should be sought; under some circumstances a modified lottery will be the most appropriate device to select subjects.

Combinations of known and unknown risk of physical or psychological harm--2

Almost all research to be considered in this category is innovative therapy. However, this is, in general, innovative therapy at much more ad-

vanced stages than those activities described in the preceding section. Thus, in general, the high standards for selection of capable subjects called for in the preceding section will not be required. Devices such as community consultation and lottery systems will almost never be needed. Some special problems in this category will be exposed through examination of the special case known as the randomized clinical trial (infra). Earlier, this category was divided into two large subsets for purposes of developing guidelines.

The first subset is defined by the use of a therapeutic modality proved effective for a certain disorder in one human population which is now to be tested for safety and efficacy in different sorts of persons having the same disorder. It is the custom in the United States to develop new drugs based upon testing of their safety and efficacy almost exclusively in adults who are incapable of becoming pregnant. The reasons for this were presented to the Commission during its deliberations on research on the fetus and have been discussed in detail by Capron (20), Mirkin (26), and Shirkey (25, at p. 827 et seq). As a consequence, most drugs must contain on their FDA-approved package labels a statement to the effect that their safety and/or efficacy have not been established in children and/or pregnant women. In fact, it might be more appropriate to include in such statements that the safety and/or efficacy of the drug has not been established in women who are capable of becoming pregnant.

When a drug that has been proved safe and effective in the adult male and infertile adult female population is used either in children or in fertile or pregnant adult females, such use is attended by the risks discovered through testing in the preceding populations. These are the known risks of such use. In addition, there may be unknown risks which are discovered only through use

in the new populations. A clear case in point is thalidomide which was found to be very safe and very effective as a sleeping pill in non-pregnant adults. Other drugs known to be reasonably safe in adults were found to be highly toxic to infants; eg, chloramphenicol.

It is common practice in this country to administer drugs approved for use in non-pregnant adults to pregnant women and children. Such administration is conducted according to the usual standards of medical practice without rigorous testing of safety and/or efficacy. In this way we have a tendency to distribute the unknown risks of such activities not randomly but rather capriciously. In addition, we have no assurance that, should the risks materialize as harm, they will be detected.

As noted earlier, in this subset of this category of research, it may ordinarily be assumed that the benefits identified in other populations of humans will accrue to the new population in which the drug is used. Thus, if a pregnant woman or a child is afflicted with an illness that threatens to cause either death or permanent disability, almost no-one would challenge the right of that person to be treated with a drug that might produce a cure. For example, such a person might have a serious infection with an organism that is sensitive to (capable of being killed or having its growth arrested by) an antibiotic not proved safe or effective in such persons. It seems appropriate in such cases to administer the antibiotic.

When the treatment is symptomatic, greater problems are presented to those responsible for making decisions. If the child or pregnant woman is not threatened with death or disability, does that person have the right to assume unknown risk on behalf of himself or her fetus? In other words, does that person have the moral obligation to endure pain, nausea, insomnia, and

so on, in order to avoid unknown risk of physical or psychological harm? Many persons in this category choose to take the symptomatic remedy (26). Whether they are aware of the unknown risk they are assuming is uncertain; it seems safe to guess that in most cases they are not.

The dimensions of this problem--particularly as it relates to drug therapy in pregnant women and children--have been explored in detail by Mirkin (26). He points out, for example, that the effects of drugs that influence the central nervous system (eg, tranquilizers, sleeping pills, sedatives, analgesics, alcohol, and so on) on behavioral development are virtually totally unknown. Yet, approximately 32 per cent of pregnant women take tranquilizers during the course of their pregnancies.

Parenthetically, it should be emphasized that such "unapproved" use of drugs must rarely be associated with substantial harm; if it were commonly associated we would probably be much more aware of it. What we must be alert for is the extraordinary toxicity. A mechanism should be devised for early detection of such toxicities as those associated with administration of thalidomide to pregnant women and chloramphenicol to infants. Yet, this mechanism should not deprive individuals in such populations of their usual expectation of usually equivalent benefit in exchange for usually equivalent risk.

In general, new drugs--and other modalities where appropriate--should be tested very carefully in animals in such a way as to be able to anticipate toxicities peculiar to developing humans. Assuming that animal testing produces no cause to suspect toxicities peculiar to developing humans, the following general formulation might be appropriate. Although the preceding discussion has focused primarily on problems peculiar to developing humans,

the following formulation is intended to be applicable to this entire subset of this category of research.

General formulation: When a therapeutic modality that has been proved safe and effective for the treatment of a disorder in one class of humans is to be used for the therapy of the same disorder in another class of humans, selection of individuals in the new population to receive the therapeutic modality may closely approximate the standards used in the determination of therapy in the context of practice. The patient-subjects should be informed that there is, in general, a remote possibility of unknown physical or psychological harm. They should further be informed that if they choose to receive the therapeutic modality they incur the reciprocal obligation of assuming the inconvenience of tests for safety and/or efficacy in persons like them.

The second subset of this category of research--testing for efficacy of a therapeutic modality in a disease other than that for which it was proved safe and effective--differs from the preceding subset on one important respect. There are no grounds for equivalent assumptions of benefit. The standards for selection of subjects for this subset should be closer to those for research presenting unknown risk than those for the first subset of this category. Persons having the new disease in which efficacy is to be tested should be as like as possible the population in which safety has been established. However, if the new disease for which the modality seems effective is one which if untreated may cause death or serious disability and if there are no suitable alternative methods of treatment, it may be appropriate to proceed rapidly to introduce use of this modality in populations differing substantially from that in which safety has been established.

The randomized clinical trial (RCT): The RCT is a special case of research which presents combinations of known and unknown risks to the subjects. The RCT--which is being used with increasing frequency in the United States--is the subject of an extensive analysis by Fried (10). The known risks of the RCT are those of the various modalities that are being compared. The unknown risks include, among other things, the fact that there is an approximately 50 per cent chance (if two modalities are being compared) that a subject will learn retrospectively that he has been treated with the less effective modality. The RCT usually is conducted with the dual purposes of bringing direct health-related benefit to the patient-subject and learning how to better benefit like persons in the future.

Fried suggests that, for a variety of reasons, the RCT is used much more often than is necessary. He suggests that this overuse is related to the high priority given by scientists to statistical truth--particularly when they cannot achieve theoretical truth. I shall agree that the device of the RCT tends to be overused and attempt to develop a guideline that would tend to limit its use to cases in which it is necessary. If the assumption that the RCT is overused is not correct, this guideline will not particularly reduce the frequency with which it is used.

Guideline: An RCT should be conducted only when there exists a legitimate question as to which of two or more competing modes of therapy (including prophylaxis) is superior. Evaluation of superiority may take into account either considerations of safety or of efficacy but usually both.

The effect of this guideline would be to rule out the RCT to test the relative safety or efficacy of a modality against placebo in the treatment

of conditions for which there exist accepted or standard modes of therapy. In such cases the new modality should be tested for superiority against the accepted standard.

Fried suggests that the RCT tends to exploit the administrative availability of certain types of prospective subjects (10, at p. 63, eg):

"Thus, for instance, Veterans Administration (VA) hospitals have been particularly apt places for the conduct of RCT's, because of the comprehensive nature of the records they keep, the fact that patients moving from one part of the country to another could be kept within the experiment, and because administrative coordination between many hospitals is particularly convenient, thus leading to more valid, general results."

As noted earlier, the RCT has some features in common with social policy research. This becomes particularly true when an institution such as the VA offers the RCT as the only mode of therapy for a given condition. Thus, the following guideline is suggested:

Guideline: Establishment of a RCT within an institution requires that the prospective subject population have made available to them the alternative of personal care according to standard and accepted practice within the community. If the prospective subject population is one which has no reasonable alternatives available--eg, patients at a Veterans Administration hospital, military hospital, the only hospital in a town, and so on--and if no alternative to participation in the RCT will be offered within the institution, community consent is required. (However, as noted earlier, in this case community consent does not override the necessity for individual informed consent.)

Fried further suggests that in many types of RCT the patient-subject is obliged to sacrifice whatever he perceives as good in the traditional physician-patient relationship (10, eg at pp. 160-165). Fried suggests that

one way of partially resolving this problem is to exclude primary care physicians from conduct of and participation in RCTs. In his perception, tertiary care physicians do not ordinarily enter into physician-patient relationships; consequently, they should be assigned responsibility for conduct of RCTs including the random allocation of various individuals to the alternative modes of therapy. I disagree. Many tertiary care physicians enter into long-term physician-patient relationships. In those sorts of RCTs in which the services of a tertiary care physician who does not enter into long-term physician-patient relationships are required, the same degree of short-term involvement with the tertiary care physician would ensure in the context of either practice or the RCT. Thus, when a surgical procedure is compared to drug therapy for a condition, the surgeon is likely to be involved in the care of those referred to him for the same amount of time whether he is proceeding in the context of practice or RCT.

Guideline: RCTs should be conducted so as to preserve--to the extent possible--the personal physician-patient relationship. This will ordinarily mean that the patient-subject can identify one member of the RCT team as his personal physician to whom he can turn for various aspects of personal care. Alternatively, the patient-subject should be encouraged to maintain a doctor-patient relationship with a physician not involved in the RCT but sufficiently familiar with it to integrate its components and objectives with those of personal care.

As a corollary to the preceding problem, Fried suggests that the system of random allocation to treatment groups may often override the patient-subject's personal value systems (10, at p. 153 et seq):

"Even in medically equivalent cases, patients may have quite different value systems; their life plans may have quite different structures. And though the overall prognosis, the overall expected value of the two therapies may be practically the same, the composition of the risks and benefits of each therapy might be different. Thus, for instance, surgery for heart disease in some cases might involve a very high initial risk of surgical mortality followed by a very good risk for, say, five years of survival after the surgery, while the standard medical treatment for the same condition might have the same overall mortality expectation, but with a risk of death distributed much more evenly over the period of years."

Many other examples might be given and, have been in preceding papers (1-2). The following guideline is offered as a partial solution to this problem.

Guideline: In the design of a RCT, if there is a reason to believe that the prospective patient-subject population might have strong preferences between competing modes of therapy based upon personal value systems and even when the competing modalities seem medically equivalent, priority should be given to the personal value systems of the prospective patient-subject.

Thus, if the prospective subject has a strong wish for one of the two competing modalities based upon personal preference, he should be allowed the right to select. In the example cited above from Fried, the patient would be allowed to select between heart surgery and medical therapy. It is feasible--though less efficient--to develop suitable statistical comparisons retrospectively based upon matched pairings. Even in such cases a certain number of prospective patient-subjects may express a wish to be divested of the burdens of decision-making; accordingly, they may request that their therapy be decided by lot. When there is any reasonable question that choices between competing modalities might be based upon personal preferences, community consultation is advised.

This guideline would present a particular problem to the development of RCTs which are dependent upon double-blind design. Fried cites one example

of a RCT that was conducted as a double-blind study in which it seems to me that some of the patient-subjects might have chosen to be in one or another group based upon personal value systems. This is the study of antihypertensive therapy in which one group received placebo and the other, drugs that were known to produce such side effects as depression, fatigability, and impairment of sexual function (10, at pp. 144-145). Given the assumption of equivalent probability of benefit (without which the RCT is unjustified), it seems to me that many persons would choose not to risk the known side effects of the drugs. As it turned out, in that particular study, those who received the drugs not only survived longer but also had a much lower incidence of some of the serious complications of hypertension. However, as observed by many commentators, the ethics of a particular research project cannot be determined after the fact based upon the results. I would still propose that the personal value systems of the individual prospective subjects should take priority over the requirements of scientific design. Such studies would most appropriately be done on prospective patient-subjects who either have no choice based upon personal value systems or wish to be divested of the burdens of such decision-making.

Known risk of physical or psychological harm--2

As this category has been defined it excludes innovative therapy. When a procedure is performed with the intent of bringing direct benefit to the individual upon whom it is performed and the risks of the procedure are sufficiently well known to merit classification by the social device of accepted or approved (in the population of which the individual is legitimately a member), the procedure is classified as practice. Thus, in this

category it is necessary to consider only basic research. Ordinarily, this research will be designed to develop general information about the biology or behavior of a class of human beings. In some cases, the results of the research might form the basis for the development of innovative therapy for that class of human beings.

Some guidelines for the selection of subjects for this category of research were presented earlier (cf, Known risk).

Guidelines: Research presenting known risk of physical or psychological harm to individuals with the expectation that the benefits of the research will accrue not to the individuals but to the class of humans they represent should be conducted according to the highest possible standards of informed consent; only the most capable subjects who will permit testing of the hypothesis should be selected. If there is any reasonable doubt--as perceived by the IRB--that the class of humans will not regard the potential benefits as justifying the known risks, community consultation should be required. At the discretion of the community, a lottery system should be devised for selection of research subjects; no person should be used as a subject unless he or his legal guardian consents to his participation in the lottery.

In some cases community consultation will be desired but the actual prospective subject population may be so fragile that they cannot be assembled as a group. Alternatively, it may be necessary to initiate the proposed research on individuals who develop the biologic attributes necessary to test the hypothesis very shortly before the research must be begun. In such cases, surrogate consultation may be of value.

A good illustrative example of a situation in which surrogate consultation might be of value was presented earlier (3, at pp. 48-52). This proposal presented the known risks of coronary sinus catheterization to individuals shortly after their admissions to coronary care units with known or suspected myocardial infarctions. The purpose of the research was to develop information that might be of benefit to the class of persons having acute myocardial infarctions. Obviously, it is impossible to assemble this group of people to learn whether they perceive the potential benefits as meriting the risks to a small number of them.

In this case the surrogate group could be composed of people who had been discharged recently from coronary care units in which they were hospitalized for treatment of myocardial infarction. Such persons ordinarily will be aware of the fact that they are at relatively high risk of sustaining additional myocardial infarctions. This group might be asked if they consider the potential benefits of the proposed research to be sufficient to merit the risk presented to even a small number of them. Further, if they were to be readmitted to a coronary care unit with another myocardial infarction, would they consent to participation in the research (given the conditions detailed earlier)?

If a large percentage of the surrogates answered yes to both questions, the IRB could proceed with confidence to approve this proposal given all of the precautions cited in the initial description of the project.

SUMMARY AND CONCLUSIONS

Principle: The subjects of research shall have those attributes that will

permit adequate testing of the hypothesis. In most biomedical and in some behavioral research the attributes can (and should) be stated precisely in biological terms. In some behavioral and in most social research, the attributes can (and should) be stated in social terms. An adequate statement of those biological and/or social attributes that establishes a universe of prospective subjects includes criteria for exclusion as well as inclusion.

This principle establishes criteria for selection of subjects based upon the requirements of the scientific design of research; however, it has far-reaching implications in the protection of the rights, health, and welfare of humans including many who are not subjects of research. This principle is meant to have priority over any subsequently stated criteria for selection of subjects.

In many studies it is necessary to include in the subject population individuals who are commonly called "normal controls" or "healthy volunteers"; there are no such persons. Normality and health are states of being that cannot be proved scientifically. Thus, it is ordinarily preferred to describe these individuals as being free of certain specific attributes of non-health or non-normality.

One exclusion from this principle is suggested by acknowledging that some types of research have no specific hypotheses (eg, some pilot studies) and that in some types of research the hypotheses evolve during its early conduct. Ordinarily, these studies should present no risk (infra) to the subjects.

Research categorized by nature of risks

For purposes of developing guidelines, research is categorized by whether or not it presents risk and, if so, what sort and to whom. It is

acknowledged that in many cases the nature of both the benefits and the beneficiaries is of equal importance; in general, the nature of the benefits is used to establish subsets of research in categories defined by the nature of the risk. There are five major categories of research determined by risk criteria:

1) Research presenting mere inconvenience to the subject: Research which presents the subject with the necessity of bearing the burden of mere inconvenience is distinguished from that which presents the possibility of consequential injury (determined as a function of probability and magnitude). Research in this category employs techniques, modalities, and interventions that have been tested sufficiently to earn the classification (by the social device) of accepted or approved (for either research or practice purposes). Research presenting mere inconvenience is characterized as presenting no greater risk of consequential injury to the subject than that inherent in his particular life situation (only as the life situation relates to the research).

The next three categories of research present known and/or unknown risks of physical or psychological harm to individual subjects; in these categories, possibilities of social, legal, and economic harm are disregarded:

2) Research presenting unknown risk of physical or psychological harm: Research conducted in this category employs techniques, modalities, or interventions which have not been performed sufficiently often or well in humans to permit reasonable assessments of the probability and magnitude of harm they might produce. This category includes most innovative therapies (practices) at the earliest stages of their development.

3) Research presenting known risk of physical or psychological harm: Research considered in this category employs techniques, modalities, and interventions that have been tested sufficiently well to predict with reasonable certainty both the probability and magnitude of physical or psychological harm to the prospective subject population. The probability and/or magnitude of physical and/or psychological harm is greater than that inherent in the prospective subject's life situation.

4) Research presenting combinations of known and unknown risk of physical or psychological harm: The most important type of research in this category is innovative therapy in which the therapy has been proved safe and effective in one human population and which is to be tested for safety and/or efficacy in another. The differences in these populations are determined by such biological attributes as age, sex, pregnancy, and altered states of physiology that are either induced deliberately (eg, by co-administration of another drug) or are naturally occurring (eg, presence of a different disease).

Three guidelines are proposed for the category of known risk which are designed to minimize the possibility of physical or psychological harm. These guidelines are equally applicable to unknown risk research in which there is some reason to suspect consequential injury; eg, based upon prior animal testing or toxicities determined in preceding populations.

Guidelines: a) Every possible effort should be made to convert known risk of physical or psychological harm to mere inconvenience. b) Utmost effort should be made to identify those individuals most susceptible to harm for purposes of excluding them from the prospective subject population.

c) Research should be conducted only by investigators who are highly skilled in the early detection and minimization of developing or nascent harms. The facilities immediately available to them to accomplish these purposes should be the best known.

Before proceeding to discuss either the risks that are borne by groups (category 5) or the evaluation of benefits from the perspective of the groups it is necessary to identify four devices that might be utilized.

Community consent is defined as informed consent negotiated with the community in which it is planned to conduct research or from which it is planned to draw prospective subjects. The elements of informed consent to be negotiated with the community are each of those eleven that are germane to the proposed research.

The community may consent to overriding the necessity for individual informed consent for several categories of research. These include social policy research which requires arbitrary allocation of material goods as well as saturation involvement of the community, and research involving some types of inconvenience. The community may not consent to imposing known and/or unknown risks of physical or psychological harm on one of its members without the consent of that member.

Community consultation is distinguished from community consent; it involves consultation with the community in which it is planned to conduct research or from which it is planned to draw prospective subjects. In general, the function of community consultation is to assist the investigator in learning how to better conduct his negotiations for informed consent with individuals within the community. In cases in which individuals are asked

to assume known or unknown risk of physical or psychological harm and in which the potential benefits are expected to accrue more to the class of persons than to the individual research subject, through community consultation it may be learned whether the class perceives the potential benefits as being worthy of assuming the risks of research by even a small proportion of their class. Another purpose of community consultation is to reduce the fragility of individuals who are either highly vulnerable or highly dependent in their negotiations with investigators. Community consultation will also be advised for establishing lottery systems (infra).

Surrogate consent is defined as informed consent negotiated with a group of individuals that is in all important respects (biologically and/or socially) virtually identical to the actual proposed research subject population. This device is used in situations in which approaching the actual proposed subject population with full information would defeat the purposes of the research. The elements of informed consent to be negotiated with the surrogates are each of those eleven that are germane to the proposed research. Surrogate consent is said to have been achieved when a sufficient number of surrogates (say, 95 per cent) state that given full information they would have consented to become research subjects. In contrast to community consent, surrogate consent can never be used to authorize research in the absence of individual or proxy informed consent. However, based upon the availability of surrogate consent, the IRB may decide that it is permissible to proceed with some categories of research without individual or proxy informed consent; eg, unseen observer research.

Surrogate consultation is distinguished from surrogate consent in that the surrogates are not virtually identical to the actual proposed subject population. Surrogate consultation is used in cases in which community consultation might be desired but the actual proposed subjects are either too uncomprehending or too vulnerable to provide such consultation. The surrogates should be the closest approximation that is reasonably possible (biologically and/or socially) of the actual proposed research subject population.

Various procedures may be employed, depending upon the purposes and the populations, to negotiate or achieve community^{and} surrogate consent or consultation; model procedures are proposed in appropriate sections.

5) Risks borne by society, institutions, or classes of people: In general, when it is a group that will be put at risk, informed consent should be obtained from the group through community consent.

Social policy research--conscious and systematic experiments designed to yield results useful in the formulation of public policy, where this intervention involves a sample of the human population and sometimes a control group--often involves the arbitrary allocation of material goods to a segment of the population and measuring in some formal way the effects of such allocation on the recipients. Often, a control group that is as similar as possible is studied to see how well they fare without having been recipients of the material goods.

Proposed guideline: In social policy research involving the arbitrary allocation of material goods to one segment of the population and measuring in some formal way the effects of such allocation on the recipients, community

consent is required. If there are control subjects (individuals who will be similarly studied but who will not receive the material goods) they are to be considered part of the community from which consent is required.

In general, it is assumed that the community (or collection of communities) will be unable to discover any mechanism for allocation of the goods that they will agree is more just than a lottery.

Some additional guidelines are proposed for selection of subjects for research that presents risks to groups.

Proposed guideline: In research that presents substantial risks to society, institutions, or classes of people, community consent is required.

The nature of the research is nearly irrelevant; it may be basic biological, biomedical, behavioral, or social research. The main criteria for establishing this class of research is that in the view of the IRB either:

- a) The risks to the group in the aggregate are substantial and are greater than are likely to be perceived by any individual member of the group; or
- b) There is likely to be difference of opinion within the group as to whether the results of the research might be detrimental to the group.

In this category of research there is usually a requirement for negotiating informed consent with each individual. This requirement may be waived only if both of the following requirements are met: a) There is no consequential risk of physical or psychological harm to any individual; and b) The group according to its own established rules of procedure determines that there is no necessity for each individual to consent.

Proposed guideline for undisclosed purpose research: If in the view of the IRB, there is reasonable probability that a prospective subject population

would not consent to undisclosed purpose research if the purpose were disclosed in advance, the IRB should propose a suitable mechanism for obtaining surrogate consent.

Proposed guideline for unseen observer research: If in the view of the IRB, there is reasonable probability that a prospective subject population would not consent to unseen observer research if they were made aware of the fact of its existence, the IRB should propose a suitable mechanism for obtaining surrogate consent.

Some additional problems are identified in which there might be conflicts of interest between individuals or groups as to whether it is appropriate to proceed with a particular research proposal; no guidelines are offered for their resolution. Conflicts of interest may be between society in general on one hand, and on the other, groups of individuals who might be perceived as enemies of society. Conflicts are not limited to social research. For example, in studies of the pathogenesis, prevalence, or incidence of occupational diseases there are often conflicts between management and labor as to whether the research should be done. Another type of conflict of interest is created when--in the course of conducting research--there are unexpected findings that may be so harmful to a group that, perhaps, they should not be published.

INCAPABLE SUBJECTS are defined as those lacking sufficient power, prowess, intelligence, or resources to either perform or accomplish: a) Participation in the research, or b) The protection of their own rights and welfare. The major focus of the discussion of incapable subjects is on identifying those who are incapable of protection of their own rights and welfare. These individuals are further classified as follows: 1) Un-

comprehending; 2) Vulnerable; and 3) Dependent. These categories are not exclusive sets; some guidelines developed for the protection of those in one category are equally applicable for protection of those in another.

The uncomprehending subject is classified as incapable largely by virtue of being unable to comprehend the information necessary to provide valid consent. The following are general formulations for the development of guidelines for the selection of uncomprehending subjects:

a) In those who are intermittently or predictably inebriated or unconscious, consent can usually be negotiated in advance. If there is some cause to suspect that one's judgment might change while inebriated, it should be negotiated in advance whether the change in judgment is to be honored. More specifically, the person who expects to become inebriated may consent to have his judgment while not inebriated take priority over any expressions to the contrary while inebriated.

b) In developing guidelines to participate in research that presents mere inconvenience, standards for comprehension should not be set too high. If they are, it will tend to exclude inappropriately some persons from assuming the role of subject as a job. In general, it should be assumed that a person is capable of suitable comprehension unless this is demonstrably not the case. When in doubt, comprehension can be assured with the aid of third party scrutiny or the 2-part consent form.

c) In developing guidelines to participate in research that presents known and/or unknown risk of physical or psychological harm, standards for comprehension should be set rather high. To the extent that the benefits of

such research will accrue more to the class of persons represented by the subject than directly to the uncomprehending subject there should be an increasing presumption of the necessity for third party scrutiny or the 2-part consent form.

d) In cases in which the intervention is categorized as innovative therapy and in which the physician-investigator and the IRB agree that this is as good as the best alternative therapy (innovative or otherwise) for a well-defined category of prospective subjects, if neither direct nor proxy consent is possible, consent may be presumed.

e) The truly uncomprehending subject is, in general, not a suitable prospective subject for research unless the only individuals that possess the biological attributes necessary to test the hypothesis are necessarily also uncomprehending. In such cases it will be necessary to have suitable proxy consent. In cases in which there might be difficult choices between reasonable alternatives and in cases in which known and/or unknown risk is assumed by individuals with a primary purpose of benefitting their class rather than with an expectation of direct health-related benefit, it may be appropriate to establish mechanisms for consultation with the community of proxies. In some cases it might be appropriate to establish mechanisms for surrogate consultation.

2) Vulnerable subjects are defined as those who are either capable of being wounded or defenseless against injury. Vulnerable individuals are categorized further into two groups each deriving its vulnerability from different origins; these are: A) The sick; and B) The impoverished. A third category is developed as the potentially vulnerable: C) Minorities.

A) For present purposes, sickness is defined as a state as perceived and defined by the individual assuming the sick role. It is a state which the individual would abandon--with the aid of technically competent help--in favor of a condition that he would perceive as healthy or at least as more healthy than he is.

Among those who are vulnerable by virtue of being sick, several categories are viewed as being highly vulnerable. Persons having prolonged chronic illnesses which are refractory to standard therapeutic modalities and persons who question their self-worth are viewed as seriously vulnerable. Perhaps the most vulnerable are some persons who believe (correctly or incorrectly) that their own death is imminent.

Recently, it has been proposed that a new class of subject called the "neomort" might be developed. A neomort is an individual who has been declared dead by virtue of current criteria for establishing brain death and whose other bodily functions are maintained with the aid of various devices. Such persons might be maintained indefinitely for a variety of biological research procedures that for various reasons one might not wish to perform on sentient beings. Additionally, organs and tissues might be harvested as necessary for transplant purposes. The neomort proposal is merely identified as an issue that the Commission might wish to consider; no guidelines are proposed.

General considerations for the development of guidelines to select subjects who are vulnerable by virtue of being sick:

a) Persons having prolonged chronic illnesses which are refractory to standard therapeutic modalities are particularly vulnerable to taking risks even for remote possibilities of relief when they perceive themselves

as desperate. Such persons are most likely to be protected by requirements that all innovative therapies are to be conducted according to the highest standards of the relevant scientific discipline. This presumes that they will first be reviewed by an IRB which will have sufficient expertise to review the proposed innovative therapy for scientific merit.

b) Persons who question their self-worth may be especially vulnerable to inappropriate inducement by offering benefits other than those directly related to their health. Thus, it seems appropriate that the guidelines reflect a need for caution not to exploit such persons. On the other hand, advice given to those responsible for selection of subjects should not be too rigid. Some persons, by virtue of being excluded, might have their senses of self-esteem diminished further.

c) The most difficult group with which to deal will be those who perceive themselves as dying. Some of these persons are particularly susceptible to loneliness; inappropriate exclusion of such persons from "normal human activities" might intensify such feelings. Thus it would be clearly inappropriate to develop rigid guidelines excluding dying persons from research characterized by mere inconvenience.

In general, research on dying persons which presents known and/or unknown risk should be limited to that in which the dying person--or at least that class of persons which he represents--is likely to receive direct health-related benefits. Experiments designed to use the dying person merely because there is no further way of causing him damage--particularly when these are done without meticulous negotiations for informed consent--are an affront to the dignity of such persons.

On the other hand, guidelines should not be so rigid as to proscribe altruistic acts done with meticulously negotiated informed consent such as donation of an organ or tissue according to the provisions of the Uniform Anatomical Gift Act.

d) Those who are vulnerable by virtue of having assumed the sick role are, in general, the most suitable subjects for most biomedical research. To the extent that the research is done with the intent of bringing direct health related benefits to the subject this seems to present little problem. A greater problem is presented when sick persons are asked to assume risk with the expectation that the benefits will redound more to the class of persons whom they represent than to themselves. In estimating the potential benefits of research to a class of persons, the investigator is likely to err, if at all, on the side of overestimating. The individual sick person tends not to be strategically placed either to disagree with the investigator's estimate or to refuse an appeal to do good for others. In research presenting known risk and in some categories of research presenting unknown risk (where there is some cause to presume that the unknown risk might be substantial) and the purpose of the research is to develop information that is more likely to benefit the class than the individual, community consultation is required. The class of persons who will receive the benefits is better situated than either the investigator or the individual prospective subject to decide whether the benefits are sufficiently great that they would wish to expose even a small number of their class to the known or unknown risks. In some cases it may be appropriate to establish lottery systems to determine who will be the subjects of such research (infra). In some cases the proposed subject popu-

lation may be so fragile that surrogate consultation may be required.

e) In some cases there will be competition for scarce innovative therapies; the most fair way to determine who shall be the recipients among those having equal medical needs is a lottery.

B) The impoverished: Impoverishment is defined as a condition in which a person considers it necessary to take extraordinary risks to secure money or other economic benefits that will enable him to purchase what he considers to be the necessities of life. Further, his willingness to take extraordinary risks is based upon his belief that he cannot secure a sufficient amount of money by ordinary means. This category intersects, but is not identical with, that of being dependent by virtue of being on welfare.

Proposed guideline: Economic inducements to participate in research should be determined by the amount of inconvenience to be imposed on the subject and should not be based on calculations of known or unknown risk. As a corollary to this guideline it might be stated that research subjects should not be paid to assume risk; they should rather be compensated for injury.

This guideline, if adopted, would represent a departure from the tradition in our society that persons are commonly paid high salaries to assume large risks. Therefore, in order to justify adoption of this guideline it will be necessary to provide justification for this departure from tradition.

General formulation of another guideline to protect the impoverished:
In calculating the costs of health services to an individual who will simul-

taneously play the roles of subject and patient, it should be calculated how much his medical care would have cost had he not agreed to play the role of subject. This amount should be paid by the patient. The additional costs incurred as a consequence of agreeing to play the role of subject should be paid by the investigator or sponsoring agency.

C) Minority groups. Individuals who are members of minority groups (as determined by race, sex, ethnicity, and so on) are not to be considered particularly vulnerable a priori. Because the group may be the subject of discriminatory societal customs, an inordinately high percentage of the group may be classified as uncomprehending, vulnerable, or dependent by virtue of other criteria. Such persons should be treated accordingly. The interests of members of minority groups are probably best protected by representation on the IRB.

3) The dependent subject is defined as one who is unable to exist, sustain himself, or act suitably or normally without the assistance or direction of another or others. He is connected in a subordinate relationship to another person or institution.

In considering the problems of developing guidelines for the selection of dependent subjects, discussion is focused on dependent relationships that present either of two potentials. The first is that by virtue of the relationship, the dependent individual is administratively more available to the investigator to be selected as a subject than are other individuals not having the same dependent status. The second is that in which the dependent individual might fear that he might forfeit either in part or in whole his dependent status by virtue of refusing to become a subject. Related to the second potential--but also having its roots in the barriers to autonomy

identified in connection with the sick role--is the concept of the fragility of the individual who is either highly dependent or highly vulnerable (by virtue of having assumed the sick role). The notion of fragility suggests the relative lack of power such persons have in negotiating with investigators.

General considerations for the development of guidelines: In general, it is appropriate to draw upon the administratively available to assume inconvenience. However, in research presenting risk of physical or psychological harm, as the degree of risk increases, there should be a decreasing assumption of the validity of drawing upon the administratively available. In situations in which known risk is presented in order to develop basic information that will be ^{of} presumed benefit to the class, there will be a decreasing assumption of the appropriateness of drawing upon the administratively available without consulting them as a group. Thus, in some cases it will be necessary to seek community consultation and in others, community consent.

In general, it is not appropriate to threaten individuals with loss of dependent status owing to unwillingness to assume known and/or unknown risk of physical or psychological harm; rare exceptions are specified subsequently (infra).

In general, it should be assumed that most persons can choose to receive an innovative therapy. However, the choice to receive an innovative therapy imposes upon the individual the reciprocal obligation of assuming the inconvenience of tests necessary to prove its safety and/or efficacy. In cases in which the innovative therapy is scarce, refusal to assume this reciprocal obligation may justify exclusion of that individual. However, a distinction

must be made between depriving a person of a single modality on the one hand and, on the other, of an entire dependent relationship. It is not appropriate to terminate a professional-client relationship because the client refuses to be the subject of research--including innovative therapy.

The issue of developing a system for compensation of harmed research subjects is reviewed in some detail. Development of a suitable system would yield several salutary effects to the entire research process. It will be most difficult to develop appropriate guidelines for the selection of subjects for research presenting known and/or unknown risk without having first developed suitable systems for compensation. The proposals for guidelines for selection of subjects contained in this paper are based on the assumption that appropriate mechanisms for compensation of harmed subjects will be developed.

A proposal for the development of lottery systems to distribute some sorts of known and unknown research risks is presented. The proposal has the following features. Built into it is a device for securing community consultation to determine whether the group as a group perceives the potential benefits of the research as being sufficient to merit the presentation of the risks to even a small number of them. It is suggested that an assembly of prospective subjects would tend to reduce the fragility of the individual negotiating as an individual with the more powerful professional. This system might also be used to minimize the possibility of exploitation of the administratively available. Entry into the lottery would be validated only by the informed consent of the individual.

It would be most appropriate to use this form of lottery in the very early stages of an innovative therapy in those cases in which there is some cause to suspect that there might be substantial risk. It would also be appropriate to use this system in research presenting known risk with no immediate prospect of direct health-related benefit.

Categories of research reexamined

Proposed guideline: In research presenting mere inconvenience--but neither known nor unknown risk of physical or psychological harm--all humans may be considered appropriate subjects providing that:

a) The subjects have sufficient capacity to comprehend not only to give suitable consent to become a subject but also to perform the duties expected of a subject. Truly uncomprehending subjects should be used only if no other class of humans possesses the needed biological attributes; in such cases, proxy consent is required.

b) Refusal to become a subject will not jeopardize a dependent relationship desired by the subject; exceptions may be justified by community consent of those sharing the dependent relationship. In general, these exceptions should be allowed only when the proposed research is clearly in the interests of improving the institution.

Most research presenting social or legal risks to the individual will not become manifest as harm unless there are violations of confidentiality. In most cases, safeguards of confidentiality can be established to the extent that all concerned can be very confident that there will be no violations.

Thus, most research dealing with confidential information can be considered as presenting mere inconvenience. Where there are barriers to preservation of the confidentiality--legal or otherwise--the research might be considered as presenting known risk.

General formulation for guidelines: In research presenting social or legal risks to the individual which might become manifest through violations of confidentiality it is the responsibility of the investigator to inform the prospective subject of the extent to which confidentiality can be assured. If the investigator can assure absolute protection of confidentiality the research is to be considered as presenting mere inconvenience. In such cases the investigator assumes responsibility (liability) for any social or legal harm done to the subject as a consequence of failure to maintain confidentiality.

If there are barriers to preservation of confidentiality these should be disclosed to the prospective subject. The prospective subject assumes the risk of the consequences of violations of confidentiality through mechanisms of which he has been forewarned.

Some potential disadvantages of these guidelines are discussed.

Some additional guidelines for research presenting unknown risk of physical or psychological harm are presented: In research activities entailing unknown risk all reasonable effort should be made to conjoin the direct health interests of the subjects to the ends of the research. This guideline is most easily applicable in conducting activities that have been defined as innovative therapy.

If this guideline is adopted it would change drastically the ways in which new drugs are developed in the United States. It would be tantamount

to saying that most Phase I drug testing is inappropriate. It would not particularly change the approach to research in any other category of innovative therapy.

Some sorts of research present truly unknown risks and are not designed to bring direct health benefit to particular subjects. In general, it should be possible to identify prospective subject populations whose interests most closely approximate those of the research. Alternatively, it should be possible to identify individuals who experience similar conditions as will be created for research purposes in the course of their usual activities. An example is given of a type of research that might be conducted in this category that is necessary to establish a new class of employment. This suggests the exclusion to the earlier stated general formulation for guidelines for the selection of dependent subjects. There are some rare cases in which research presenting known and/or unknown risk is necessary to establish a new class of employment; in such cases it may be appropriate to offer such employment contingent upon an individual's willingness to be a subject of such research. Choices of who shall be the first, and so on, would be resolved most fairly through a lottery; in this case, participation in the lottery would not be voluntary.

Some special cases of unknown risk research are presented: These develop when, in the course of medical practice, use of a standard prophylactic, diagnostic, or therapeutic modality seems to be associated with a severe adverse reaction in a class of persons. Further, it is impossible to determine whether this class of persons is peculiarly susceptible to the severe complication without further research in this group. This special case is accommodated in the following general formulation.

General formulation for guidelines for research presenting unknown risk: The category of research presenting unknown risk of physical or psychological harm includes most activities classified as innovative therapy (practice) at the very earliest stages of their development. The most suitable subjects for such research are those who are vulnerable by virtue of being sick. In general, subjects for this category of research should be the most capable available having the biological attributes necessary to test the hypothesis. In cases in which there is some a priori reason to predict serious harm--eg, as in the special case cited above--community consultation should be sought; under some circumstances a modified lottery system will be the most appropriate device to select subjects.

Research presenting combinations of known and unknown risk of physical or psychological harm: Almost all research considered in this category is innovative therapy. However, this is, in general, innovative therapy at much more advanced stages than those activities characterized as presenting unknown risk. Thus, in general, the high standards for selection of capable subjects called for in that category should not be required. Devices such as community consultation and lottery systems will almost never be needed.

One subset of research in this category is defined by the use of a therapeutic modality proved effective for a certain disorder in one human population which is now to be tested for safety and efficacy in different sorts of persons having the same disorder. In consideration of selection of subjects for this subset it is argued that decisions may be based upon assumptions of equivalent benefit accruing to the new population. Also, in

this subset, there is a usual assumption of nearly equivalent risk. While there is no way to predict the extraordinary unknown harm, such harms are rare. On these bases the following general formulation is proposed.

General formulation: When a therapeutic modality that has been proved safe and effective for the treatment of a disorder in one class of humans is to be used for the therapy of the same disorder in another class of humans, selection of individuals in the new population to receive the therapeutic modality may closely approximate the standards used for the determination of therapy in the context of practice. The patient-subjects should be informed that there is, in general, a remote possibility of unknown physical or psychological harm. They should further be informed that if they choose to receive the therapeutic modality, they incur the reciprocal obligation of assuming the inconvenience of tests for safety in persons like them.

The second subset of this category of research--testing for efficacy of a therapeutic modality in a disease other than that for which it was proved safe and effective--differs from the preceding subset in one important respect. There are no grounds for equivalent assumptions of benefit. The standards for selection of subjects for this subset should be closer to those for research presenting unknown risk than those for the first subset of this category. Those persons having the new disease in which efficacy is to be tested should be as like as possible the population in which safety has been established.

The randomized clinical trial (RCT) is a special case of research presenting combinations of known and unknown risks to the subject. Careful examination of this special case provides the basis for some proposed guide-

lines some of which may be applicable to other categories of research presenting known and/or unknown risk of physical or psychological harm.

Proposed guidelines: a) An RCT should be conducted only when there exists a legitimate question as to which of two or more competing modes of therapy (including prophylaxis) is superior. Evaluation of superiority may take into account either considerations of safety or of efficacy but usually both.

The effect of this guideline would be to rule out the RCT to test the relative safety or efficacy of a modality against placebo in the treatment of conditions for which there exist accepted standard modes of therapy.

b) Establishment of a RCT within an institution requires that the prospective subject population have made available to them the alternative of personal care according to standard and accepted practice within the community. If the prospective subject population is one which has not reasonable alternatives available--eg, patients at a Veterans Administration hospital, military hospital, the only hospital in town, and so on--and if no alternative to participation in the RCT will be offered within the institution, community consent is required. (However, as noted earlier, in this case community consent does not override the necessity for individual informed consent.

c) RCTs should be conducted so as to preserve--to the extent possible--the personal physician-patient relationship. This will ordinarily mean that the patient-subject can identify one member of the RCT team as his personal physician to whom he can turn for various aspects of personal care. Alternatively, the patient-subject should be encouraged to maintain a doctor-patient relationship with a physician not involved in the RCT but sufficiently familiar

with it to integrate its components and objectives with those of personal care.

d) In the design of a RCT, if there is a reason to believe that the prospective patient-subject population might have strong preferences between competing modes of therapy based upon personal value systems and even when the competing modalities seem medically equivalent, priority should be given to the personal value systems of the prospective patient-subject.

Mechanisms for the implementation of these guidelines, their implications, and some of the problems they create are discussed.

Research presenting known risk of physical or psychological harm--as it has been defined in this paper--excludes innovative therapy.

Proposed guideline: Research presenting known risk of physical or psychological harm to individuals with the expectation that the benefits of the research will accrue not to the individual but to the class of humans they represent should be conducted according to the highest possible standards of informed consent; only the most capable subjects who will permit testing of the hypothesis should be selected. If there is any reasonable doubt--as perceived by the IRB--that the class of humans will not regard the potential benefits as justifying the known risks, community consultation should be required. At the discretion of the community, a lottery system should be devised for selection of research subjects; no person should be used as a subject unless he or his legal guardian consents to participation in the lottery.

In some cases, community consultation will be desired but the actual prospective subject population may be so fragile that they cannot be as-

sembled as a group. In other cases, it is necessary to initiate the research on individuals who become very ill or otherwise develop the biological attributes necessary to test the hypothesis very shortly before the research must be begun (thus, there is no time for community consultation). In such cases, surrogate consultation may be of value.

In developing guidelines for the selection of individual research subjects, the most difficult problems are presented by those types of research that present substantial risk to the individual with the hope of developing information that will be of benefit primarily (or only) to the class of humans he represents. Such research presents two very difficult questions. The first--which we now have no way to answer--is: Does the class of humans consider the hoped for benefits sufficient to merit the risk to be borne by even a small fraction of its members? Assuming that this can be answered affirmatively, the second is: Which individuals shall assume the risks?

The devices and procedures proposed in this paper for obtaining the opinions of groups are designed to answer both questions. Ordinarily, if the answer to the first question is yes, the second would be resolved most fairly through a lottery.

It must be understood that these devices and procedures are untested. They may or may not accomplish the purposes for which they are intended. Even if they do, they might be so cumbersome and expensive that they might not be worth using. If it is decided to implement these suggestions, their initial trials should be conducted in such a way as to provide an accurate

assessment of their costs and benefits.

Meanwhile, these devices and procedures--if they are to be used at all--should not be used capriciously. They should be used only to resolve legitimate and important problems. The necessity for their use should be determined by the IRB on a protocol by protocol basis.

Finally, the vast majority of research should call upon reasonably capable subjects either to assume only inconvenience or, alternatively, to accept reasonably predictable risks in exchange for reasonably predictable direct health benefits. Thus, in most cases there should be no need to solicit group opinion (or consent) or to establish lottery systems to select research subjects.

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II

BASIC ETHICAL PRINCIPLES RELATING TO
RESEARCH INVOLVING HUMAN SUBJECTS

5

ETHICAL PRINCIPLES AND THEIR VALIDITY

Kurt Baier, D. Phil.

ETHICAL PRINCIPLES AND THEIR VALIDITY

(1) The Problem. The National Commission for the Protection of Human Subjects was asked to "identify the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects." The task assigned to me is (i) to provide guidelines for identifying ethical principles and ethical reasoning generally and for distinguishing them from other kinds of reasoning which also bears on the acceptability or inadmissibility of human actions; (ii) to provide guidelines for identifying such other kinds of principles and reasonings, e.g., those employing legal or technical, esthetic or political considerations, and to explain the inter-relationship between all these types of principles and reasonings; and (iii) to describe and comment briefly on the range of thought among contemporary philosophers regarding the identification of principles and the evaluation of their validity.

The task presents formidable difficulties of selection and organization, particularly since it is to be accomplished within the confines of a paper of reasonable length and readability. I have made every effort in this brief survey and critique of the great variety of approaches and mutually conflicting, confusing, meagre and inconclusive contemporary writings on the problems raised by the Commission, not to give undue weight and credibility to those views with which I myself sympathize. All the same, given the current state of the field, my own perspective on the problem inevitably will not only have colored my own answers, however qualified and non-committal, to these difficult questions, but probably also even my selection and presentation of the materials examined.

The essay is organized under four heads. Section I contains a brief survey and critical discussion of the way a number of contemporary philosophers, in what is generally regarded as the mainstream of Anglo-American thought on the subject, have viewed the problems posed. From this discussion it emerges that moral reasoning is now widely viewed as a special form of practical reasoning, but that there are major disagreements about precisely how this form of reasoning is to be characterized, and even about whether any kind of objective or neutral investigation can settle these disagreements. The remaining three Sections, II-IV, are given over to the task of providing as objective or neutral a characterization as is possible of moral reasoning and of how it differs from other forms of practical reasoning. More specifically, Section II is a preliminary but indispensable excursus into the nature of practical reasoning; Section III sets out the peculiarities of moral reasoning with occasional asides, where apposite, about its significant differences from neighboring forms of practical reasoning; and finally, Section IV, attempts to provide whatever objective guidelines it seemed possible to give about how to recognize ethical principles and test their validity, as well as how to avoid confusing ethical with other types of practical principles.

I. Current Views

(2) There is general agreement that certain forms of words, "Non-therapeutic experimentation on aborted fetuses is morally wrong," "To experiment on these children putting them at risk for the sake of future gains to humanity was unjust," "The neglect of one's professional duties is repre-

hensible," "it was wrong of you to criticize me in front of these people" normally express moral judgments.¹ But there is a good deal of disagreement and doubt about others, e.g., "knowledge is intrinsically good," "honesty is the best policy," "you are impertinent," "that was a mean thing to do."

(2.1) Ethical Terms and Ethical Judgments. It is therefore natural to ask what it is in such judgments that makes them ethical. During this century four major answers have been given to this question. Some, e.g., G.E. Moore,² or W.D. Ross,³ locate it in the fact that these judgments attribute to things certain quite extraordinary properties, with which ethics is properly concerned. The main objections to such theories are that it is impossible to detect or ascertain in any reliable way the presence of these unusual properties and that even if that were not so, the mere fact that things or even actions have certain properties does not of itself provide a reason why anyone should therefore act in one way rather than another. But to provide such reason is surely the main business of ethics. And so this account of what it is that makes a judgment ethical is, at best, inadequate.

Therefore, some later theorists, such as the Emotivists⁴ and Prescriptivists,⁵ rejected peculiar ethical properties and located the ethical in the peculiar function of ethical judgments: the Emotivists in their expressive and evocative, the Prescriptivists in their imperatival or action-guiding function. The two main objections to these theories are (i) that they misleadingly restrict the ethical to one or other of the many linguistic functions all of which are performed by ethical judgments in one context or another,

but which are equally performed by non-ethical judgments. (Thus, while "You thief!" typically expresses feeling, it does not guide action, and while "You ought to pay not later than four weeks after delivery" guides action, it does not express feeling nor evoke it, and "If he had not delivered on time, you need not have payed him" does neither.) (i) They leave out what is an essential feature of the language of ethics, namely, that it comprises a form of practical reasoning, leading to conclusions which may but need not provide action-guidance for some particular agent. (Thus, "If she had become pregnant, it would have been his moral duty to marry her" hints at some underlying moral reasoning but comes too late to provide guidance.)

A fourth school,⁶ therefore, locates the ethical in the peculiar form of reasoning on which certain judgments are based. One of the most widely acclaimed theories, that of R.M. Hare,⁷ combines elements of the third and fourth schools. He maintains that what makes judgments ethical is the fact that they are prescriptive and universalizable, and that these two features generate a peculiar form of reasoning, requiring its own peculiar logic, the logic of imperatives.

It seems fair to say that there is, at this time, very widespread agreement that it is at least a necessary, if not a sufficient condition, of a judgment's being ethical, that it should be capable of being supported by a certain method of reasoning. The main disagreements within this broad consensus concern the precise nature of this method of reasoning.⁸

(2.2) Theoretical and Practical Reasons. It is generally agreed that moral reasoning is practical as opposed to theoretical, and that the difference

is of considerable importance.⁹ It is, for instance, often claimed that G.E. Moore's ethical theories are vitiated by his failure to realize that the business of ethics was practical rather than theoretical, that ethical judgments had practical functions, such as action-guiding, and that to the extent to which they were capable of being supported by reasoning, the reasoning had to be practical rather than theoretical. The difference can be put in this way. Practical reasons are practical in two important senses. In the first place, they are practical in the sense of being "justificatory," or as I prefer to say, "normative," rather than "explanatory" or "probative." I prefer normative to justificatory because practical reasons are used not only in justification but also in deliberation. Thus, the reasons we employ in practical reasoning are reasons to (i.e., reasons why someone should) believe, desire, want, feel, prefer or do something, rather than (explanatory) reasons why, someone in fact believes, desires, etc., something, or why something has happened, has certain properties, or exists, or (probative) reasons showing that these things are as claimed. They are, therefore, reasons concerning matters over which we have some direct or indirect control, and employed in contexts in which there is a question of how to exercise this control, rather than a question of simply taking cognizance of the matter.

These reasons are, however, practical also in the sense that they are used in determining what someone should do rather than what he should believe. The reasons employed in such reasoning are reasons for action, that is, they are only one particular sub-class of the larger class of normative reasons.

The assumption that moral thinking, reasoning, and arguing is practical in this double sense rests on the further assumption that the central and most

important question in ethics is practical, i.e., (what someone should do, morally speaking, or) what, morally speaking, is the right thing for him to do. This assumption is made by the classical and dominant tradition in ethical theory and I shall accept it here without argument. But there are thinkers^{9a} who regard as central another question, namely, what is a morally good person? On such an approach, it is not so clear that moral reasoning and thinking is essentially and primarily practical in the sense explained.

(2.3) Meta-ethical inquiries into the nature of morality. There is, however, a second line of inquiry which intersects with and complicates the line already sketched. It sets out from the thought that, though the moral thinking of individuals and groups has peculiarities distinguishing one such morality from another, yet such social and individual moralities are recognizable as moralities, and distinguishable from legal systems, religions, customs, manners, and so forth. Why not then, this line of inquiry insists, look for the common and peculiar characteristics of such recognizable moralities, if we want to find out what, if anything, is the function of moral judgments, moral reasoning, and moral talk generally?

We can divide the responses to this question into three groups. The first is skeptical. It says that "morality" has so many different senses that no useful purpose can be served in unraveling them.¹⁰

The second maintains that "morality" is not univocal, though the number of senses is manageably small, so that there is something to be gained by clarifying them.¹¹ Most frequently only two senses are found, a social and a personal one. Morality in the first sense is a system of generally known and

applicable principles, rules, or precepts, usually tied to a particular social order, which those subject to it recognize as binding on them. In the second sense, a morality is the set of principles, precepts, or particular dictates coming from one's own conscience, reason, intuition, or moral sense, which one recognizes on that account as absolutely binding on one, though not on anyone else.

The third concedes that "morality" may have several senses--it admits, for instance, that while in one sense it is the opposite of "immorality," in a second sense it contrasts with "law," "religion," "manners," etc.,--but maintains that the relevant (i.e., the second) sense is univocal, and that with proper care, an investigation of that sense can bring to light the true nature and function of morality. However, those who take this last line then disagree with one another on what such a careful, unbiased investigation does bring to light. We can distinguish three major positions.

The first yields the widest sense of "morality."¹² On this view, a morality is that set of principles, rules, precepts and dictates which the society or individual in fact recognizes as supreme and as overriding all others. It has been objected to this view that it lets in too much. On this view, it is said, law and religion and a person's strongest commitments (e.g., to obey the Fuhrer, to destroy the Jews), all count as part of morality, and this is implausible.

The second view¹³ says that in listing the essential characteristics of a morality we are defining "morality." But if such a definition is to be "neutral," and not simply a covert and illegitimate way of smuggling in sub-

stantive moral conclusions on the pretence of linguistic investigation, then the definition has to be purely formal. That is to say, it must not include as part of the definition any object or goal or purpose or function of morality. For that would be to abandon the neutral stance appropriate to one who is trying to illuminate the domain of morality, when this is not the opposite of immorality, but of law, religion, art, etiquette, expediency, or wisdom. As an instance of this type of theory we can again mention that of R.M. Hare. For he holds that we can say of a person, or a group, that he or it has a morality if and only if they have a set of principles, rules, or precepts which they regard as universalizable and prescriptive, as well as overriding.

The main objections to the two additional criteria, have been these. The objections and their sympathizers¹⁴ maintain that there are moral judgments, such as those of supererogation, which are not universalizable. If I conclude that I ought to give 50% of my income to charity I do not necessarily imply that everyone else in my position ought to. I may realize that we cannot demand these things of each other but only of ourselves. The other objection has come from those, who like the Ethical Egoists, maintain that universalizability is not a truly formal, because not a truly neutral criterion. For some if not all versions of Ethical Egoism preclude the universalizability of ethical judgments. If as an Egoist I argue that I should make an exception in my favor, I am not implying that everyone else should do also, i.e., make an exception in his favor for that might, and normally would, not be in my best interest. Those who live by Ethical Egoism are therefore excluded from having a morality. Their Egoistic reasoning is, by this definition, implied to be

overridden by conclusions of universalizable, i.e., ethical reasoning. In this way a substantive ethical conclusion is derived from this definition of "morality," which is not therefore a truly formal one. Any definition of "morality" which adds any criterion to that of overridingness is thus non-neutral in that it gives a higher place in the hierarchy of types of practical reasoning to the type that satisfies these additional criteria than to the types that do not.

The main objection to including prescriptivity in the definition of "morality" is as follows. If prescriptivity means no more than guiding action, then it is innocuous but also superfluous. For a morality must in any case contain directives which people can use in solving their practical problems. If, however, it means more, e.g., what Hare means by it, then it is objectionable because it mischaracterizes moral judgment. Hare means two things by "prescriptivity." The first is that if someone makes a prescriptive judgment, then he tells someone to do something, he intends the person to whom it is addressed to do what he tells him to do. But this is simply not true of moral judgments. Thus, if on hearing the full story, I now judge in my mind that a certain person morally ought to have told the full truth in a certain matter, then this certainly does not imply that I now intend that other person to have told the truth (for that does not even make sense), nor does it imply that I intended him to do so at the time when, as I now judge, he ought to have told the truth.

The second thing Hare means by "prescriptivity"¹⁵ is that if someone accepts a prescriptive judgment addressed to him, then he must act in accord-

ance with it or at least set himself to do so. And this also is false. For I may quite honestly think that I ought to do something here and now, say, terminate life support to a terminal patient and yet not do it, nor intend to do it, nor set myself to do it.

However, the most serious objection to formal definitions such as Hare's comes from a third type which offers "material" definitions. Such theories¹⁶ maintain that "morality" must be defined as in some sense social. Some define "morality" in terms of a social function, such as the promotion of social harmony or the promotion of general welfare. Others say that to be a morality, a set of principles and rules must contain at least directives for the settlement of interpersonal conflicts of interests, and directives requiring everyone's consideration of the interests of at least some others than himself.

On such material definitions of "morality" certain sets of principles would not be considered moralities, even if they satisfied the three formal criteria mentioned in the previous discussion. Consider the following three principles: (i) Always to get out of bed left foot first, (ii) Never to pick one's nose in public, (iii) To surround oneself as much as possible with beautiful objects. Now if someone treated these principles as supreme, universalizable, and prescriptive, then this set would satisfy the three criteria of Hare's formal definition but, supporters of material definitions would argue this would not be a morality. To many people, including myself, this seems a telling point.

The most interesting and deepest-cutting difficulties, however, have come to light when one examines various material definitions. Such examina-

tions put the spotlight on another belief about morality which has been commonplace at least since Kant. It is the belief that moral judgments are rational not only in the sense that they are valid conclusions of certain forms of argumentation, but also in the sense that they provide anyone with adequate reason to act in accordance with them and against acting contrary to them, even if they run counter to our inclinations and our interest. This is one of the implications of the Kantian claim that they are "categorical imperatives." But this belief causes problems for material definitions. For it seems that if one accepts a material definition, then the question of whether one has reason to follow the conclusions of one's moral arguments becomes a contingent matter. For one then does not necessarily have reason to do what such judgments require, particularly when they conflict with one's self-interest or one's desires. If the function of morality is the promotion of social harmony, and if I do not care much about social harmony, then I may often have no adequate reason to follow the principles of morality rather than those of self-interest or simply my desires.

One way out of this difficulty, which has recently been suggested,¹⁷ is to drop the categoricity requirement in definitions of a morality. This still leaves us free to regard moral principles and judgments as not merely spelling out ways of attaining our preexisting ends. We can think of them as somewhat like the rules of chess which we have reason to follow because we want to play chess, or the canons of good manners, because we want to be well mannered. In these cases, we follow these rules not for the prizes which following them may gain us, but for its own sake, the sake of doing that doing which consists in following these rules. On this model, the rules of morality are the con-

stitutive rules of an "autotelic" activity.

However, this way out is open to a serious objection. It turns morality into a practice with principles and precepts which a person has reason to follow only if he wants or likes to engage in that sort of activity. If he does not, there is no reason why he should follow these principles. Yet, when we think about the principles and judgments of a morality, it does seem plain to us that we have reason to demand of others and they of us that we all adhere to these principles.

A second way out is to say that the principles of morality and the canons of self-interest always coincide. But apart from making morality unnecessary, this solution is quite certainly false in the world as we know it. Our brief examination of Prisoner's Dilemma in Sections II and III below, should make this plausible. It would be a third way out of the difficulty if it were the case that the basic ethical principles are such that from their very nature they ought to be regarded as overriding the reasons of self-interest. If this way out were possible, we could think of the principles and precepts of morality both as categorical and as satisfying all the requirements of formal theories. Whether they could also satisfy the material requirements would depend on precisely what content, if any, we can or must give to moral principles which can satisfy the requirements of categoricity.

If the line of thought sketched so far is sound, then it is most plausible to conceive of a morality as a form of practical reasoning transmitted and taught by societies, for use by individuals in the solution of their practical problems, beginning (in deliberation) from general principles to

specific conclusions solving personal practical problems, conclusions which are rightly regarded as overriding the conclusions arrived at by all other forms of practical reasoning, including self-interested reasoning.

Our next aim should therefore be to provide a characterization of the relevant features of practical reasoning in general and the place of self-interested reasoning in it. This would put us in a position to see whether there really are any principles which from their very nature ought to be regarded as overriding all other reasons including reasons of self-interest, and if so, whether there are any other reasons for accepting the account of moral reasoning implied by this third line of thought.

II. Practical Reasoning

(3.1) Thinking without language. There is a kind of practical thinking which does not depend on the thinker's having a language or having grown up within a culture. Many of the higher animals are generally believed to be capable of this kind of thinking or problem-solving. They are assumed to be capable of perceiving certain situations in which they find themselves, as posing "practical problems" and certain developments in which they are involved, as "solutions to these problems." A cat in a puzzle box trying to find its way out, a squirrel eyeing a bird feeder, Koehler's famous ape reaching for the bananas outside his cage, would be examples of animals in such recognized problem situations. One can say that what makes these situations problematic for these animals is that they want to get hold of or do something but that they do not know how. Their practical thinking consists or manifests itself

in their intelligent goal-directed behavior, whether their intelligence shows itself merely in the recognition of a development as a solution and in the ability to learn from their experience to improve the problem-solving performance (as in the case of cats in puzzle boxes or rats in mazes), or whether intelligence is also exhibited in the economy or even ingenuity of the attempted solutions (as in the case of Koehler's ape).

Such practical thinking is severely limited in scope. What the individual has learned cannot be communicated to others. There is therefore no scope for advice, or for joint and thus more effective thinking. Each individual and each generation must start from scratch. They cannot profit from the experience of others, or only in the most limited way, e.g., demonstrating how something is done, as when a cat shows her kittens how to trap and catch a bird.

(3.2) Practical Reasoning. The presence of a language introduces into practical thinking four powerful new factors for growth. The first is the possibility of accumulating and storing practical knowledge based on the experience of many different individuals and even generations in a given group culture.

The second factor is making this knowledge available to group members through education in the form of publicly available general directives, such as principles, rules, maxims, precepts, and the like, and by teaching them the skill of applying them to their individual practical problems.

The third factor, arising directly out of the second, is the availability of practical knowledge with the status of intersubjective validity. An indivi-

dual learning to apply the publicly available general directives to himself and his special situation, learns pari passu to apply them, mutatis mutandis, also to others in relevantly similar situations. He must learn to move in thought from the most general principles, such as "Always do unto others as you would have them do unto you," "Always do what is in your own best interest," "Never give a sucker an even break," and so on, down to "therefore, do this here and now," whether it is his own case or that of another. He must, in other words, learn what are the relevant similarities and differences between the different cases. Obviously, if there is to be such practical thinking, the general directives on which it rests will have to be formulated in such a way that they are capable of being employed by individuals of different types and in different situations. Such general usability of a general directive will be a condition of incorporation in the culture of a group. By "practical reasoning," we ordinarily mean this sophisticated practical thinking based on such general directives. It is because animals lack such general directives that the practical thinking of animals does not amount to practical reasoning.

The fourth new factor is the possibility of a conflict between reason, i.e., the outcome of such practical thinking and inclination. A person engaging in practical reasoning, may arrive at conclusions, i.e., answers to the question of what he should do, which direct him to do something he is not inclined, or is inclined not, to do. Thus, I may find, in the mousetrap I have set up in the kitchen, a mouse injured but still alive. My strong inclination may be to run and leave the mouse to its fate. However, practical reasoning based on certain principles to which I subscribe, e.g., "Never inflict or allow avoidable suffering," may lead me to conclude that I ought

to take the mouse out of the trap and kill it quickly and painlessly. Again, my inclination may be to light a cigarette, but reasoning based on principles such as "Never unnecessarily endanger your health" may lead me to conclude that I ought never to smoke again.

(3.3) Theoretical and Practical Tasks. Concerning each practical question, "What should N do?", there is thus what we might call a "theoretical" and a "practical" task. The theoretical task consists in applying the relevant publicly available general directives to the problem in hand, and terminates in a particular practical judgment of the form "N should do A," where this has a degree of specificity sufficient to enable N to translate the judgment into action. "N ought never to smoke again" or "N ought to take the mouse out of the trap," etc. "N ought always to do others as he would have them do to him" does not have for normal adults the requisite specificity.

There is an obvious but important difference between N's theoretical and his practical task. The former can be performed by anyone with the relevant knowledge, whether he is N himself or someone else. But the practical task can be performed only by N himself. If, let us say, N's wife takes the mouse out of the trap for him and kills it quickly with a well-aimed blow of a hammer, she either has not performed N's practical task or the practical task was not as described. If N ought to have taken the mouse out, her taking it out is not the performance of N's practical task. If her taking it out was the performance of the practical task in hand, then the outcome of the theoretical task must have been, not "N should take out the mouse etc.," but perhaps "N should see to it that the mouse is quickly taken out (by whomever)" or "Someone in the kitchen should take out the mouse" etc.

Once there are publicly available general directives for use in practical thinking then there is the possibility that N arrives by a correct application of these principles to his case, at the judgment that he ought to do A, but then does something else instead. Thus N may think that the publicly recognized general directives applicable to his case are principles of sound practical reasoning and he may in applying them to his case arrive at the same judgment that anyone else, applying them correctly would arrive at, namely, that N ought to do A, yet he may then not do what he recognizes as having the weight of reason behind it.

(3.4) Considerations and Reasons. We must therefore distinguish between what I shall call "practical considerations" and "practical reasons," respectively. Suppose I come to believe both F_1 , that smoking causes lung cancer, and F_2 , that giving up smoking will disrupt my work. And suppose also that when I attend to F_1 , I am inclined to quit smoking, but when I attend to F_2 , I am inclined to continue. Then F_1 is for me a consideration in favor of quitting, and F_2 a consideration in favor of continuing. But now suppose that when I attend for some time to both F_1 and F_2 , then I decide to give up smoking. Then although F_1 and F_2 are for me considerations relevant to whether or not to give up smoking, F_1 is a weightier consideration than F_2 , for when attending to both, F_1 inclines me more strongly in favor of quitting than F_2 inclines me in favor of continuing.

Reasons differ in an important respect from considerations. If F_1 is a reason to quite smoking, then if I know or believe F_1 , I ought to be inclined to quit smoking, quite irrespective of whether I actually attend to it adequately, and whether, supposing I do so attend, I then am so inclined. And

similarly, if F_1 is a weightier reason for giving up smoking than F_2 is for continuing, then I ought to be more strongly inclined to quit than to continue; and I ought to be so inclined quite irrespective of whether I adequately attend to both F_1 and F_2 , and irrespective of whether, supposing I so attend, I then am so inclined.

There is thus no contradiction in saying that F_2 is for N a weightier consideration than F_1 , but F_1 is a weightier reason than F_2 . It is even possible that F_1 is for N a consideration against, although it is in fact a reason for, quitting. What makes a fact a consideration and a weightier one than another fact, is thus a totally different matter from what makes a fact a reason, and a weightier reason than another fact. Making a mistake about what is for someone a consideration in favor of doing A, is simply a mistake about his psychology: about what would weigh with him, and how strongly, in what circumstances. Making a mistake about what is a reason to do A is not such a simple psychological matter, but presupposes a different sort of theory about what makes facts reasons. To believe, correctly or mistakenly, that a certain fact constitutes a reason to do A, implies that such a fact ought to weigh with one in favor of doing A, that one ought therefore to be disposed to do A, even if one does not come naturally to be inclined to do A simply by attending to this fact. Obviously, such a theory of reason is designed to give practical reasoners guidance about what to do which is based on a knowledge of what is a reason, and not on some psychological self-experiment. We can now turn to a discussion of a few popular theories of practical reasons.

(4) Theories of Practical Reasons. Theories of this type are tied to standards of rationality. We judge a person or his behavior to be rational

or irrational according as he, or it, does or does not measure up to certain demands about the performance of the theoretical and the practical tasks. Before indicating what these standards are, we must mention some features of this practice of evaluating people by these standards.

(4.1) Performance and social pressure. People have an interest in knowing about any given individual with whom they have dealings, how well he performs his theoretical and practical tasks. For just what dealings they may be willing to enter into with him may depend on just how reliable is his performance of these tasks. It is, now, therefore surprising that we find a widespread practice of evaluating others on this basis and, when asked (sometimes even when not asked), to transmit such judgments to third parties. In view of the recognized importance of this task, people also monitor their own performance and try to maintain the required standards of rationality.

In some types of practical reasoning, morality being the most obvious case, society will not be satisfied with letting the individual choose whether to keep his performance up to the mark and reap the benefits or let his standards slip and take the consequences. In these cases society attempts in various ways to ensure the general maintenance of the minimal standard. The two most widely used methods are training and sanctions. We not merely teach the young the difference between right and wrong but also try to inculcate in them "a good will," that is, a readiness to perform their tasks adequately, even in the face of contrary inclination. The imposition of sanctions has brought in its train the widespread practice of requiring practical reasoners to justify themselves, that is, to be able to rebut accusations that they have not adequately performed their tasks. We shall note that

though in all forms of practical reasoning, there will be a tendency, on account of the importance of the matter, for practical reasoners to justify themselves when they are accused--no one likes to be thought a fool or a knave--it is only in relation to certain forms of practical reasoning, morality being again the prime case, that success at justification is a condition of not suffering the relevant sanctions. We do think that in moral matters it is not solely up to the individual reasoner whether or not he wants to perform the theoretical and practical tasks adequately. By contrast, though we have an interest in knowing how imprudent or foolish our fellows are, we would hardly wish to insist, or allow others to insist, that members of the community be forced to be less imprudent or foolish--except perhaps in those special cases in which important interests of others are also affected.

(4.2) Perfect Rationality. We can now return to the various standards of rationality, by which we assess the performance of practical reasoners. The sense of "rational" which is relevant to this investigation is the opposite of "irrational," not "non-rational."¹⁸ In this sense, a rational, i.e., a not irrational, being is one whose reasoning does not fall below a certain standard of excellence. Ordinarily this standard is quite low. One has to perform very poorly indeed to qualify as irrational. Thus, failing to make the effort to rid oneself of one's tendency to overeat when one is overweight and has a heart condition which is adversely affected by overweight, is contrary to reason but not necessarily irrational. The reasons against making the effort--say, it would disrupt one's work--may be quite weighty enough to save one's failure from being irrational, even though of course these reasons will not be as weighty as those in favor of making the effort.

There is, however, another sense of "rationality," namely, "perfect rationality" which implies a higher standard. In this sense it is used of a person whose behavior is always in accordance with reason, behavior which the agent has adequate reason to think has the weight of reason behind it. In this paper, "rationality" always means perfect rationality.

However, "rationality" in this sense cannot be applied to anything until the notion of a practical reason has been further clarified. Up to now, we have skirted the central problem, namely, that of spelling out what it is to believe that a fact about a certain course of action constitutes a reason to enter on that course of action. I briefly sketch three widely held theories of practical reason:

(4.3) Informed Inclination. The simplest kind of theory, and one which appears to be widely held,¹⁹ at least by implication, simply declares that what are, for a person, considerations are also reasons for him. That is to say, rationality consists in always acting in accordance with one's informed inclination. It should be noted that this is a genuine theory of reasons, not merely a rejection of reasons in favor of considerations. The difference is important, for belief in considerations does not commit one to anything beyond psychological explanatory theory. A theory of reasons by contrast, is an evaluative theory (Cf. above (2.2)). It ties the excellence of a person's performance of the theoretical and practical tasks to the evaluation of a person as rational or irrational, or in other ways excellent or defective.

On this simple view, rationality need never involve acting contrary to inclination. Such unpleasantness can always be avoided, at least in principle, by taking the trouble to attend adequately to all the facts. Now, of course, this may be a different if not an impossible task. And if it cannot be performed, then an individual who knows what facts are for him considerations, might still have to act contrary to his current inclination, since if he were able adequately to attend to the facts, his inclinations would presumably be different from what they now are.

What kind of assistance could a culture on this view give to practical reasoners? It could provide general practical directives of how people of certain types ought to act. The culture would simply spell out what are for what (psychological) types of persons, considerations in favor and against what in what sorts of circumstances, but would present these considerations as reasons.

This simple theory has several weaknesses. For one thing it suffers from the practical difficulty or impossibility of saying clearly what it is for a person to attend adequately to a given fact. For how long and in what manner must a person attend? But in the absence of such a criterion, we cannot tell what are for a given person considerations.

More interesting is the fact that such reasons are "self-anchored," in a sense still to be explained, and that the theory is therefore exposed to some of the objections to Rational Egoism, namely, those connected with Prisoners' Dilemma, which will be examined shortly (below, (4.4)).

(4.4) Rational Choice. A second theory of rationality is that found in Decision Theory.^{19a} There rationality is conceived as an evaluation of the relationship between a person's choices and his preferences. The question asked is, "Given your preferences, is it rational for you to choose A?" The principles of rationality are therefore those of rational choice. The most frequently cited principles of rational choice are (i) The principle of effective means: given that one has a certain object, one is to choose the best, i.e., the most economical means. (ii) The principle of inclusiveness: given that one has several aims or desires, one is to choose that plan which is most inclusive, i.e., promises to attain the greatest number of these objects. (iii) The principle of greater likelihood: given that one has several objects whose realization by the available means is not equally likely, one is to choose the plan which is the most likely to succeed.²⁰

This notion of rationality leaves no room for the question of whether the person's preferences, aims or objectives are themselves rational. If rationality is entirely a matter of the ways in which we can achieve ends, then the choice of ends or the possession of preferences themselves is not a matter of reason. Since it is quite natural to go on to ask whether such aims or preferences are morally justifiable, it is then only logical to exclude morality from the realm of rationality. It should be obvious, however, that this exclusion follows only because of this rather limited (though highly influential) conception of practical rationality.²¹

(4.5) Rational Egoism. A third theory offers a single criterion of what is a reason for doing something. On this view, a supposed fact about doing

A is a reason for N to do A if and only if doing A unfavorably affects N's interest, and indifferent (not a reason one way or the other) if and only if doing A does not affect N's interest either favorably or unfavorably. If F_1 is a weightier reason than F_2 , if and only if when N is confronted by a choice between doing A and doing B, doing A would more favorably affect his interest than doing B.

As a theory, Rational Egoism is in some respects more satisfactory than the two preceding ones. Even though it is difficult to say exactly what is meant by "favorably affecting someone's interest," we understand the idea well enough to employ it successfully in many cases. And it does not seem impossible to refine the concept and build up a body of practical knowledge vastly more detailed and useful than is our present conventional wisdom on the subject. Lastly, the theory is complete, in the sense that there are no practical questions or problems about which we could not in principle find an answer along the lines of Rational Egoism.

The theory does, however, have a glaring weakness, to which I have already referred. As has frequently been pointed out if people interacting with one another subscribe to this theory and know or believe of one another that they so subscribe, they thereby deprive themselves of certain benefits and so bring it about that their interest is more adversely or less favorably affected than it would be by other policies. One type of situation in which this occurs, "Prisoner's Dilemma," has been widely studied, and can be briefly described.²²

Two prisoners are accused of a joint bank robbery, as well as minor crimes separately committed. The prosecutor tells each that if they both confess the bank robbery, both get 10 years; if the first confesses and the second does not, the first gets off free, the second gets 20 years; and if neither confesses, they both get only 1 year (for their minor crimes). Supposing that their preferences are strictly parallel to the length of time in prison, then the preferences (or interest) of each ranked from highest to lowest are: (i) himself confessing and the other not confessing, i.e., himself getting off free, the other getting 20 years, (ii) neither confessing, thus both getting 1 year; (iii) both confessing, thus both getting 10 years; (iv) himself not confessing, and the other confessing, thus himself getting 20 years, the other getting off free.

Clearly, on the theory of Rational Egoism, it is rational for each to confess, for whatever the other does, he will do better if he confesses than if he does not. If the other confesses, then by confessing he will get 10 rather than 20 years. If the other does not confess, then by confessing he will get off free rather than getting off free should the other be foolish enough not to confess.

Since it is rational for both to confess, both will get 10 years. They are therefore both doing less well than if both refused to confess. But, being Rational Egoists, this policy is not available to them.

What can the Rational Egoist do in such a situation? He can do two things. (i) He can, following Hobbes, work out certain policies analogous to the policy of nonconfession which, if but only if universally adopted, would benefit

everybody more than if the policies of Rational Egoism were universally adopted. Let us call such policies "distributively beneficial," as opposed to those of the Rational Egoist which are "reflexively beneficial." The difference is that a person benefits from others following distributively beneficial policies, not from himself following them. The Rational Egoist will therefore not follow such policies. To derive the benefit of distributively beneficial policies, Rational Egoists must, therefore, (ii) create a social order, or support an already existing one, in which distributively beneficial rules are imposed as overriding the members' own individual policies of Rational Egoism, and supported by effective sanctions. In this way, the distributively beneficial rules are also made reflexively beneficial, and so can be followed by the Rational Egoist.

Thus, by creating a compulsory social order in which distributively beneficial rules are enforced, the Rational Egoist can derive these benefits not available to him in what Hobbes called the state of nature. Of course, he will have to pay his share of the cost of the enforcement machinery. To the extent that a particular Rational Egoist can detect a loophole in the social order by which he can escape the social sanction, he may even reap the double benefit (at someone else's expense) of breaking the social rule and of doing what is reflexively beneficial. He is here in the position of the prisoner who knows that the other will not confess and who can confess with impunity himself, thus getting off free, though at the expense of the other who will get 20 years.

The consequence is that the Rational Egoist has reason to set up and maintain a social order containing a system of distributively beneficial

and enforceable rules, but he cannot regard these rules as themselves constituting reasons for him to act. He has reason to obey these rules only to the extent to which obeying them coincides with following egoistic reasons. Where, through a failure of the sanctions, egoistic reasons diverge from what the rules require, it would be contrary to reason for him to follow rather than to break the rules. A theory such as the one I have just sketched may have been held by Bentham.²³

This is an impressively simple, coherent, and plausible theory of reasons. In particular, let it be noted, it does not introduce practical reasons of more than one kind, and so has no problem about the relation between egoistic and moral reasons. Nevertheless, it has two quite serious weaknesses. The first is its tendency towards absolutism, a point clearly seen and perhaps welcomed by Hobbes. For a community of Rational Egoists who know or suspect each other of Rational Egoism will have (egoistic) reason both to break the social rules when it is to their advantage to do so, and to ensure that others will never be in a position to do so. They will therefore want to ensure by the most stringent policies of "law and order" that crime does not pay other people. At the same time they will attempt by bribes and threats and other methods to bend the law to their own advantage. And the officials whose task it is to ensure that the rules are enforced will if they are Rational Egoists try to enrich themselves by bending the law, for a consideration. Of course, there nowhere are or have been communities of Rational Egoists, though it is perhaps not difficult to envisage a community in which the proportion of Rational Egoists is steadily growing so that those who are not must assume of more and more of their fellows that they are.

The second weakness is that in such a community of Rational Egoists, there is no conception of justice: no rational limit to self-aggrandisement, as Plato pointed out in the Republic. Every member of this community will therefore want to change the laws and other compulsory rules in a direction which will promote his advantage even if it is at the expense of others. And he will do it in every way, by bribes, threats, and the like, which promises success and does not unduly expose him to the risk of having the sanctions imposed on him. Thus, while the members of a community remain Rational Egoists, and cannot therefore recognize the compulsory rules of the community as constituting reasons to act in the way these rules require, they will continue to have towards each other the same egoistic attitudes they had in the state of nature. They will regard the rules of the social order as no more than obstacles in the race for self-aggrandisement. They must therefore attempt to enlarge these obstacles in the path of others and reduce them in their own paths.

It seems clear that even Rational Egoism, though an impressive theory of reasons, is by no means wholly satisfactory. The three theories so far sketched do, however, make clear that the task of a theory of reason is to yield principles following which will promote the good or, even optimal, life for people within communities, in which there are publicly recognized distributively beneficial rules which are, at least most of the time, treated as overriding the reflexively beneficial canons of self-interest. It is also plain that the worst shortcomings of Rational Egoism could be remedied by a theory of reason from which it followed that these distributively beneficial rules themselves constituted practical reasons to abide by them and sufficiently

weighty ones at that to override the canons of self-interest when the two come into conflict with each other.

Our brief survey of the activity of practical reasoning and of what is involved in saying that a certain supposed fact is a reason for someone to do a certain thing, has brought to light two important facts. The first is that practical reasoning is, from its nature, designed to override what someone is inclined to do, even when he is fully informed of the facts that affect his inclination. The second is that any account of practical reasoning is committed to some theory of what a reason is, i.e., what makes a fact a reason for someone to do something. Not even such intuitively plausible claims as that the fact that doing something is in one's best interest is a reason for him to do A is more than a hypothesis, and as our discussion of Prisoners' Dilemma showed, it is not one that is without difficulty. The main difficulty, of course, arises out of the fact easily overlooked that a person's interest is affected not only by what he does himself, but also by what other people do and by developments (such as a flood or the exhaustion of certain resources) which are not anyone's doing or at any rate not the planned outcome of human action. Therefore, if one wants one's interest affected as favorably as possible one has to take into account more than one's own policies. Hence Rational Egoism, which does not allow coordinated policies, deprives itself of one of the most effective means of getting one's interest promoted without promoting it oneself. For, as we have seen, by following distributively beneficial rules one does not in any way promote one's own interest, but if such rules are generally followed, one's interest is thereby promoted.

This flaw in the theory of Rational Egoism can be remedied if we do not construe our theory of reasons, the way Rational Egoism does, as the strong claim, that the fact that a course of action is in one's interest and only that fact is a reason for one to enter on that course. None of the difficulties sketched will arise if we drop the second half of this claim and say instead that although the fact emphasized by Rational Egoism really is a reason, it is not the only fact that is. If, for instance, we were to add to our theory the claim that the compulsory social rules, which are needed to combat the worst consequences of Rational Egoism and other self-anchored systems of reasoning, are also reasons, namely, reasons to act as these rules require, and reasons which override the reasons of self-interest, then even the secondary difficulties resulting from the general acceptance of Rational Egoism would be avoided. But, of course, such a modification would give rise to many other difficulties. For one thing, while it is plausible to say that, at least other things equal, it is rational to do what is in one's best interest, there is no plausibility whatever, especially for someone who finds Rational Egoism plausible, in this modification of Rational Egoism.

In the following section, on moral reasoning, we shall examine what a morality is, what the peculiarities of moral reasoning are, how it differs from self-interested reasoning, and whether the peculiarities of moral reasoning are designed to overcome the difficulties we have noted with self-interested reasoning, and whether it succeeds in doing so.

III. Moral Reasoning

(5) The Parts of a Culture. Our two main tasks, the clarification of

moral and other kinds of practical reasoning will be advanced if we begin by looking at the various domains of a culture in which these other kinds of reasoning are characteristically employed.

We can usefully divide the culture of a society into its theoretical, its practical, and its aesthetic part. Nothing will here be said about the aesthetic part. In the theoretical part belong its entire accumulated explanatory knowledge and belief, primarily its pure sciences. In its practical part belong its applied theoretical or technical knowledge or know-how, that is, its applied sciences, crafts, and technologies; its practical wisdom, that is, its canons of the good life; and, finally, its social order or mores, that is, the directives spelling out what the society requires or expects of its members. We shall need to ask what part or parts of a culture its morality belongs in.

(6) Technical Reasoning. This type of reasoning starts out from a set of possible ends, such as health, wealth, shelter, nutrition, clothing, power, transportation, and so on. Such possible ends are assumed, on good evidence, to be the actual ends of many people on many occasions in many different circumstances. In technical reasoning, it is merely assumed, not established that it is always or indeed ever rational to try (or not to try) to attain any of these ends. Technical reasoning is, therefore, a truncated or limited form of practical reasoning, a mere stretch or patch of it. The main idea of technical knowledge is to make publicly available such reliable stretches of practical reasoning, leaving it to individual practical reasoners in their individually different situations to determine for themselves whether it is

rational for them to try to attain such an end.

Suppose a patient suffers from severe mental deterioration and memory deficit.²⁴ Suppose his condition is diagnosed as occult hydrocephalus, which causes decreased mental abilities by interference with absorption of cerebrospinal fluid. The relevant part of the technical reasoning of the surgeon could be formulated as follows:

- (i) My task (end) is to cure this patient.
- (ii) This patient suffers from mental deterioration.
- (iii) The cause of his mental deterioration is the interference with the absorption of the cerebrospinal fluid which is brought on by occult hydrocephalus.
- (iv) If I am to cure the mental deterioration, I must stop the interference with the absorption of the fluid.
- (v) If I am to stop this interference, I must place a plastic tube through his skull to drain the cerebrospinal fluid from the brain to the vascular system.
- (vi) Therefore I must place a tube . . . etc.

In this reasoning, it is of course taken for granted that the task or end, curing a patient, is a rational one. Steps (ii) and (iii), diagnosis and determination of causal factors, are the conclusions of medical thinking, perhaps reasoning. This part belongs in the scientific, theoretical part of a culture.

Steps (iv) and (v) also rely on theoretical knowledge. However, these theoretical ingredients can be removed. Then these steps have the form, "If I am to . . . , I am to" Depending on what exactly is the theoretical background knowledge available, "I am to . . . " can be correctly replaced by

"I could ... ," or "I must ... " or "I ought to" If the only known way to stop the interference, etc., is to insert a tube, then "I must" is the correct replacement. If there are various ways, "I could ... " is the correct one. And if inserting a tube is the best of several ways, then "I ought ... " is the correct one. In this last case, where there are available alternatives the principles of rational choice (Cf. above (4.4)) determine which is the best.

Technical reasoning thus has two important features. It starts from premises which are either general, i.e., possible ends, or are particular instances of such possible ends, a particular person's (Jones') end. These premises state ends whose rationality in general or in a particular case is no more than assumed, or implied. And such technical reasoning ends with directives which are sufficiently specific to enable a person to translate them into action.²⁵

(7) Politics. A particularly important case of technical reasoning occurs in the political domain. Politics is possible only in a society which has a political order, that is, one with political institutions, that is institutions providing for the roles of government and governed. The most important general functions of government are the regulation of what people must and need not do for one another and what they must not and may do to one another, the organization and coordination of cooperative enterprises for socially important purposes, such as defense, education, transportation, welfare, and the regulation of privately initiated cooperative enterprises. Politics is the activity of trying to influence the actions and policies of government.

One type of reasoning in this domain starts from particular political ends, that is, ends of bringing about particular governmental policy changes, or maintaining particular governmental officials in power. Applied political science tries to provide the premises and principles needed for this type of reasoning.

However, what normally goes by the name of political argument, is typically a moral argument about what governmental policy ought to be. The principles needed for this kind of argument are usually discussed in political philosophy, not in political science, though the dividing line has again become somewhat fluid.

(8) Practical Wisdom. Practical reasoning aimed at practical wisdom differs from technical reasoning in that it is complete and unlimited. The conclusions at which it arrives are neither hypothetical nor truncated. They are not hypothetical, as would be an argument beginning with "Suppose my end is" And they are not truncated, as those of technical reasoning are, for they try to establish that it is rational to do a certain thing, which means that, if in doing it one has a certain end, having that end is also rational. Typically, such reasoning has a form something like the following.

- (i) It is irrational to be imprudent.
- (ii) It is imprudent to do something for which one may have to pay damages.
- (iii) One has to pay damages if one is convicted in a malpractice suit.
- (iv) One may be convicted in a malpractice suit if one conducts

experiments on a fetus scheduled for abortion, and the mother changes her mind about aborting.

(v) Therefore it is irrational to conduct such experiments.

The main difference between technical reasoning and this form of reasoning is that the aim of the former is to identify manageable ways of attaining possible or actual ends without looking into the rationality of these ends, the aim of the latter is primarily to arrive at judgments about the rationality of a given enterprise or project within the entire life plan or system of inter-related life plans. Technical reasoning goes over short stretches of frequently trodden ground, yielding detailed, reliable and economical instructions of how to get to these destinations. Practical reasoning which aims at practical wisdom yields conclusions about whether it is wise to choose certain destinations, given one's overall situation and life plan, and those of one's fellows.

(9) Mores, Custom, and Law. The third sector of the practical part of a culture is its mores or social order. In the sense in which they are the subject matter of sociology and cultural anthropology, societies necessarily have a social order but they may lack some sectors of the social order, such as law, custom, manners, morality, or etiquette. We can imagine societies so simple, as for instance the recently discovered Tasaday in the Philippines, of which it may well be true that they do not have, say, a religion or a morality, as they certainly do not have a legal order.

It is now fairly widely accepted that what we call "custom" and "law" developed out of a simpler type of social order within which these distinctions

could not be drawn.²⁶ This differentiation probably evolved together with the growth of societies beyond the extended family and the consequent need to include in the social order rules regulating social intercourse between strangers. Such regulation by undifferentiated mores has three serious defects. It is uncertain because the compulsory social requirements are not clearly stated. It is static, because there is no social institution which makes possible deliberate and speedy changes in the social order. It is ineffective, because the social pressures which support the existing social order are inefficient. The transition from a pre-legal to a legal social order occurs when these three defects are remedied by the creation of certain social recognized functions and roles: the function of determining what shall be part of the social order backed by the strongest (legal) sanctions, a function performed primarily by the legislator; the function of ascertaining whether a particular person has acted contrary to the requirements of the compulsory social order, a function primarily performed by the courts; and the function of dealing appropriately with those who have been found to have acted in this manner, a function primarily performed by the penal institutions. The mores of a society encompass a legal order if and only if it has officials who ex officio perform these tasks.

The basic judgments involved in law and custom are to the effect that certain kinds of acts or certain particular acts are contrary to law or custom, or required or permitted by it. Practical reasoners will be expected to take such judgments or supposed facts into account in their deliberations. People's social training (their "socialization") will tend to bring it about that such supposed facts are for them considerations relevant to decisions

to engage in behavior thus regulated. But such judgments have two important characteristics which, from the point of view of practical reasoning, are limitations. The first is that an action's being lawful or customary (or the opposite) is so only within a given social order and at a given time. It is not necessarily so within the same social order at another time, or within another social order at the same or another time.

The second limitation is that such facts (that a course of action is contrary to law or custom) are not necessarily in themselves reasons against such proscribed behavior. For what is law or custom in a given society at a given time is determined by the social will, the will of its members as whole--whatever the precise relation of the society's will to the will of its members. In a political society that relation is in part consciously determined by the political institutions. As we have seen in the discussion of Prisoners' Dilemma (see above, (4.5)), it is possible that no member wants to do what the law (or custom) requires him to do, say, to pay taxes or serve in the army, even if every member also wants every other member to do what the law (custom) requires of him and wants there to be such a law. Even if Rational Egoism is sound, such wants may be rational without its following that these conventional requirements come to constitute reasons for the members. Again, if moral principles constitute reasons, these conventional requirements need not necessarily be themselves reasons, for they may be unjust or in other ways contrary to reason.

Thus, reasoning which leads to judgments, that certain courses of action are unlawful or contrary to custom, in a certain sense hangs in the air. When

we have shown, by "subsumptive" reasoning (e.g., abortion is murder, or prisoners' consent is consent under duress), that a given course of action is contrary to law or custom, we still have to show that such action is contrary to reason. Most philosophers would agree that if law and custom did impose at least prima facie moral obligations, then these conventional directives would constitute at least prima facie reasons to act as they direct, but there is considerable disagreement about whether they do impose such moral obligations.²⁷ It is therefore at least doubtful whether conventional reasoning is more than truncated practical reasoning. Only a satisfactory theory of practical reasons would be able to settle this question.

Summing up our results so far, we found that there were two types of truncated practical reasoning, technical and what I called "conventional." Both argue from premises which, as experience shows, it will often be rational for people to argue from. Both types of practical reasoning require to be supplemented with reasoning from the domain of practical wisdom, i.e., the theory of practical reasons. The main difference between technical and conventional practical reasoning is that the former is by design reflexively beneficial, the latter not. By following technical reasoning, one tends to gain the benefits of attaining one's end. By following conventional reasoning, however, one tends, at best, to benefit others though, of course, general conformity may be beneficial all round.

(10) Morality. We can now turn to what is for our purposes the most important part of a culture, its morality. It is also the most difficult and the most contentious domain. In what follows I stress the rational and the social

aspect of morality. It seems to me that all the important clues point in this direction. But though the views expounded below are widely shared, I cannot pretend that they are not also widely rejected. The best that can be said for this presentation is that no one who sets out to offer a coherent account could hope to secure universal agreement.

Moral institutions resemble those of law and custom although, of course, these roles are not occupied by professional specialists: everybody can and over time does play all of them, as circumstances require. The role of moral teacher is characterized by the fact that it involves not merely the teaching of a skill, how to perform moral reasoning, but also inculcating the good will, the readiness to perform these tasks up to the required standard of performance. The central role, that of moral agent, is supported by several support roles. There is the role of moral adviser who helps the agent with his moral reasoning. There are the roles of moral watchdog, moral accuser and judge, who see to it that performers falling below the acceptable standards receive moral condemnation. There is finally the role of defender or justifier, usually but not necessarily the accused himself who can, by showing that he has performed up to the required standard, abort moral censure. Lastly and most importantly, there is the role of moral critic and reformer.

One of the important conclusions we can draw from a study of the way these roles are performed is that, unlike one's Egoistic reasoning, one's moral reasoning is a deep concern for others. In this respect it parallels one's performance of conventional reasoning, especially legal. People are taught to, not only how to, reason morally and to perform their practical tasks.

They are surrounded by performers of support roles who take an interest in how well they perform and who censure them if they fall below standard. So far, this is much like conventional reasoning and gives support to the widely held view that a society's morality is simply a part of its mores. But such a view overlooks the rational element in the way these roles are performed, and in the language in which they express their reasoning and their conclusions. When one arrives at the judgment that, say, the legislation in a certain country of experimentation on aborted but live fetuses was morally wrong, one is saying something stronger than when one claims that in a certain country such legalized experimentation is unconstitutional. One is saying not merely that such experimentation is contrary to a judgment arrived at by a form of practical reasoning concerning which group members want others to perform their theoretical and practical tasks adequately and support this demand by social sanctions. It means, in addition, that there is reason for them to demand this and to criticize anyone who performs poorly. It means, further, that if the accused admits the judgment (that it really is wrong), then he admits that the criticism was justified, that they are quite right to judge that he ought not to have done what he did. None of this follows from claiming that it really is illegal or unconstitutional. For if the law is abolished, then such experimentation ipso facto ceases to be illegal even if nothing else about such experimentation has changed. But in such a case it could not also ipso facto cease to be morally wrong.

The second point of importance emerges from the study of the role of the critic and reformer. A legal reformer may advocate changes in the law on two sorts of grounds, internal or external, to remedy two sorts of fault. The

former are specifically legal flaws from some external point of view, such as economy or justice. In the last case, the reformer is also a moral one, i.e., a reformer of the law on moral grounds--not of course a reformer of morality. Now, the important thing to note is that there can be no such reform of morality from an external point of view. It would be absurd to maintain that our morality which frowns on slavery was in need of economic reform because moralities which encourage slavery make for greater economic efficiency. I believe this point strongly suggests that we think of moral reasoning as the highest most inclusive form of practical reasoning.

This ties in with the way a moral reformer reasons. Even if he advocates moral reforms, that is, reforms of currently accepted moral convictions, he does not go outside morality. Such criticisms are always from within the moral point of view. Moral thinking and reasoning is thus not in any way limited or truncated. It is all of a piece from the most specific to the most general principles. It seems to me that it is only because of this that we can speak of our moral principles and precepts, such as "One ought not to experiment on human subjects except with their consent" or "One ought not to violate anyone's rights" or "One ought to treat others as one would have them treat one" as moral convictions, that is, as normative convictions, as normative directives which can be sound or unsound, i.e., which pass or fail to pass certain tests.

This leads to a third point. If moral reasoning is the highest type of unlimited reasoning, that is, reasoning aiming at overall practical wisdom, then its conclusions must be regarded as overriding those of all other such

types of reasoning, including those of Rational Egoism. This is, of course, one of the widely held convictions we have about moral judgments, one very strongly stressed in the moral philosophy of Kant. But if this is so, then everyone must have adequate reason to do what morally speaking he ought to do even if it runs counter to self-interest or desire or both. In other words, the precepts and principles of moral reasoning themselves constitute reasons for action, and the supreme ones at this.

It would seem to follow that the morality of a society belongs both in its mores and in its practical wisdom. We must not, therefore, think of the morality of a group as simply another sector of the mores, as is done, e.g., by the Legal Perspectives, when they construe what they call "positive morality" as parallel to law.²⁸ A less misleading way to define the locus of morality is to say that a society has a morality if it is a moral order, that is, a rationally self-correcting social order in which this rational requirement is institutionalized in the role of the moral agent as also critic and reformer, working as needed for a modification of the social order from the moral point of view, that is, the point of view of one bent on creating a social order which every member living under it has equal and adequate reason to treat as overriding all other forms of practical reasoning including Egoistic reasoning. The morality of a group thus overlaps with those parts of its mores to which the members of the group give their backing because they believe that they satisfy the requirements of morality. There is thus nothing surprising in the fact that we want to assign precepts such as "Commit no murder" both to the mores and to morality, nor in the fact that in a society in which morality is taken seriously, there is considerable disagreement among people

about what is right and wrong. The complexity of the issues and the temptation to pass off what is merely one's personal advantage as what is morally right combine to make moral agreement extremely difficult. But if this account is acceptable, it should at least be possible to recognize moral reasoning and moral argument when it occurs, however uninformed or faulty it may be.

Here we must note another important point. The morality of a group is that part of the mores of the group which its members believe will pass a certain test. We have already seen what this test is: to provide equal and adequate reason for everyone in the community to accept these principles and precepts of the mores as reasons to follow them, and as reasons overriding all others. They must in other words be such that any rational person would always follow them rather than those of any other type of reasoning with which they might come in conflict. Precisely what this means will, of course, depend on a satisfactory theory of practical reasons. But let us for argument's sake accept a limited theory of Rational Egoism, that is, one which does not insist that self-interest and only self-interest constitutes a reason. Then we can say that moral principles must be in the interest of everyone alike. This is often interpreted to mean the same as being socially just. The morality of the group would then be those elements of its mores which members of the group believe satisfy the requirements of social justice.

We can now also say what, on this view, is the difference between a group's moral principles and maxims, and sound or valid ones. Whereas the group's moral principles are those its members take to be in the interest of everyone alike, that is, just, the sound ones are those which actually are just. Again, only

a sound theory of justice can give us knowledge of what this criterion comes to. The recent work by John Rawls does show, however, that progress here is not impossible.

It remains to say, briefly, what it is for an individual to have a morality. The sense in which he can have a morality all by himself is that in which he can have a grasp of moral reasoning, its nature and function, so that he can in any moral order in which he may find himself play the various moral roles including that most important role of moral reformer. But if my account is correct, then an isolated individual who has no contact with others, such as, let us say, the last survivor on a spaceship, would not be able to employ his moral reasoning to any purpose, except perhaps to maintain those excellences, such as self-control, which are presuppositions of adequate moral performance, just in case he does later rejoin a human group.

A second consequence is that there are indeed certain things the moral agent can take with him to other societies, namely, those which are independent of social institutions, such as the moral principles which govern what one person must not or may do to another (e.g., killing, injuring), and what he must or need not do for another (e.g., attending to a sick person if he is a physician), but of course even in this realm he may find the other society to have quite different principles and precepts, and he will have to act in relation to that society in the same way as would a member who wants to reform it. He cannot simply, and without consideration of the accepted morality, follow his own moral convictions.

The third is that it is conceivable that in a group without a social order, such as Hobbes' state of nature, he will want to use his moral principles, at least those mentioned in the previous paragraph, which do not depend on the institutions of a social order. What fate he may there suffer if he acts in this way will of course depend on what these people are like. There is no reason to think that his morality will then lead to a fulfilling life. Nor can anyone in these circumstances use the moral terms, "right" and "wrong" in the way we now do. It is as if, after poison gas has killed most of the inhabitants of a country, but in some cities the traffic lights are still functioning automatically, the few motorists left asked themselves whether it would be wrong for them to cross when the signals are red.

IV. Guidelines

(11) Identifying Ethical Principles, Reasons, Objections, Arguments. If the account of morality given in Section III is correct, then we must distinguish between what a person thinks or sincerely says his moral principles etc., are and what they really are. He may make three sorts of mistakes: what he offers are not principles, etc. (but, say, only rules of thumb), they are not his (he is only paying lip service to them), and they are not moral (but prudential or technical). We need not, in this context, worry about the first two mistakes, but the third is relevant and a real possibility. Even if people can argue validly from moral principles, they may have quite mistaken views about what they are doing when they do it, and popular misconceptions of morality may seriously blind them to what is implied in their own judgments and practices. On the view outlined in Section III, moral

principles, precepts, maxims, reasons, objections, and arguments are those which are employed in moral reasoning. Moral reasoning is a form of practical reasoning which is practical reasoning from the moral point of view. One adopts that point of view when one considers one's social order as grounded by a set of supreme guiding principles for all its members, and thinks of these members as rational agents willing to be guided by such principles as long as they have reasons for doing so as good as have any of the other members, that is, as long as the principles are socially just.

The second, even more important and difficult question raised by the Commission is how we distinguish between "valid" and "invalid" (or sound/unsound) ethical principles, and so on. The answer has already been given before. Sound or valid moral principles, are those which not merely purport to provide everyone with equal and adequate reason to follow them, but really do so. Whatever is the correct answer to the question of what justice is, it will undoubtedly involve respecting everyone's moral rights. A concern with the rights of individuals affected by proposed courses of actions or policies will therefore be a strong indicator of the reasoner's reasoning from the moral point of view.

(12) A simple example will perhaps help to make this more concrete. Dr. William Smith, in the Third Academy Forum of the National Academy of Sciences, entitled Experiments and Research with Humans: Values in Conflict, 1975, p. 90, gives the following hypothetical case.

Haym's Syndrome is a disease of the joints that begins in early childhood and becomes progressively more debilitating through early adulthood, severely impairing joint function in about half the cases. The death rate among Haym's Syndrome victims is about 10 percent before age eighteen, in-

creasing throughout adulthood to about 40 percent by age forty.

All groups within the American population are at equal risk for this disease.

There is a conventional treatment that may bring symptom relief, but there is no known cure.

Several competent investigators concluded after six months of animal studies that a new drug, NAS-18, if administered continuously in high dosages could well arrest the progress of the disease.

Their animal trials, however, have also indicated several discomfoting although not serious side effects, including diarrhea and insomnia.

The investigators decided on a two-year trial at their Haym's Syndrome Clinic at University Hospital. In their NIH grant application the trial was stated to have the dual purpose of measuring the toxicity and the beneficial effects of NAS-18 and weighing them against each other.

Forty potential subjects were selected. Thirty were outpatients at the Haym's Syndrome Clinic. Of these thirty, ten were children ranging in age from five to seventeen.

One of the investigators was the staff physician at the local juvenile training school. Ten adolescents age ten to fifteen at the school had Haym's Syndrome and were therefore selected as the remaining subjects.

At their next clinic visit, each of the thirty outpatients -- twenty adults and a parent of each of the ten child subjects -- was asked to participate in the research project. One of the investigators carefully explained the following to each person:

- That NAS-18 was a new drug that had shown promising results in previous tests. It might possibly be a major breakthrough in the campaign against Haym's Syndrome, and it might lessen the subject's pain. No one, however, could be sure of this until further research was undertaken.
- That the procedure simply involved taking pills on a regular basis and that their progress would be carefully monitored.
- That previous research had indicated some chance of developing the known side effects described earlier but that there could be other, unknown side effects.

The patients and the parents of the child subjects were then given a chance to ask questions and asked to sign the standard consent form used by University Hospital. [That form follows the statement of the case.]

Parental consent was obtained for all but three of the ten training school subjects whose parents could not be located. The school's chief administrator's consent also was obtained. The subjects then met as a group with the investigator and were told that they were being asked to participate in a drug test that had been approved by the administrator. They were given the same information as the clinic patients, but they were not asked to sign a consent form. They were told that they could withdraw from the experiment at any time.

The research proceeded according to design. Half the adults and half the children were given NAS-18, the other half a placebo. Dosages for all subjects were increased periodically during the first year of the research.

Many of the subjects seemed to benefit substantially from the administration of NAS-18 -- especially the children whose disease had not progressed to its most debilitating stages. All subjects on NAS-18 experienced less pain.

However, at a dosage where NAS-18 appeared to slow the progress of the disease, five subjects developed peripheral neuropathy, three so severe they had trouble walking. The investigators took all five subjects off NAS-18 and reduced the dosage administered to the other fifteen.

Neither the remaining fifteen NAS-18 subjects nor the twenty control subjects were informed of the neuropathy. Four months later five more subjects developed peripheral neuropathy. They then were taken off the drug.

Near the end of the trial, many of the subjects whose symptoms had been most relieved told the investigators they wanted to continue NAS-18 treatments. Expecting an affirmative response, they were surprised and disappointed when told that further trials were necessary before NAS-18 could be approved as accepted treatment for Haym's Syndrome and that they could not continue on the drug after the end of the two-year trial.

At the conclusion of the experiment, all patients were taken off NAS-18, told that further research would be undertaken but not at University Hospital, and thanked them for their cooperation and help in finding what appeared to be a promising therapy for Haym's Syndrome.

Six patients who continued to show abnormal nerve conduction and signs of peripheral neuropathy continued their visits to the clinic.

In the discussion of the case, Dr. Smith then makes a number of claims about what should and should not have been done in this case. He says, for instance: "This experiment should never have been approved by the University's

Research Review Committee or funded by the National Institutes of Health. The researchers gave children a drug that was never before tested on humans. There was no need for this, and no justification. Children should not have been used until the toxicity of NAS-18 had first been tested on adults, especially since the experiment could, at best, have benefited the subjects only temporarily. Even captive children were used, and used purely for the convenience of the investigators. Institutionalized children should not have been placed at risk when other subjects were available. Three children were used without the consent of even their parents. No child, at least one whose natural or adoptive parents were not available to give informed consent, should be the subject of a non-therapeutic experiment. None of the children were themselves asked to consent. I submit that no child over seven should be placed at risk in a nontherapeutic experiment without his or her approval." (p. 92)

Several of the statements amount to formulations of principles or are straightforward applications of such principles: "Children should not be used until the toxicity of NAS-18 had first been tested on adults, especially when the experiments can benefit the subjects only temporarily." "Institutionalized children should not be placed at risk when other subjects are available." "No child over seven should be placed at risk in a nontherapeutic experiment without his or her approval."

(13) Moral and Technical Reasoning. These are low-level principles or precepts which may or may not be intended and defended as ethical ones. It would depend how Dr. White would argue for and meet objections to them.

If he had argued, for instance, that there should have been more extensive testing on animals first, that it was wasteful and inexpedient to use scarce and valuable child subjects to test the toxicity of NAS-18 when it could be done more cheaply and without unfavorable public reaction on animals, this would be a technical argument to the effect that those interested in ensuring continued research opportunities on children were going about it in a counterproductive as well as inefficient way. If, however, he had gone on to say that the experiment on children was morally unjustified because it unjustifiably and unnecessarily put children at risk, when adults or animals could have been used, then presumably he intended it as a moral principle, one not merely defensible but required from the moral point of view.

(14) Moral and Legal Reasoning. In a later comment, Dr. Smith says, "I seriously question whether any physician should be permitted to conduct a nontherapeutic experiment on his or her own patients. Certainly a research subject's health interest should always be protected by a third party not involved in the research." (p. 94) The underlying principle is, of course, "No physician ought to be permitted ... " Such a principle would presumably be defended on what has recently been called "exclusionary reasons."²⁹ The reason for advocating this principle is not, presumably, that researchers are less capable of recognizing the health interests of their subjects, or less moral, than other people, but that their research interests are in conflict with their subjects' health interests, and that this would place a considerable burden on them in performing their theoretical and practical tasks. The principle, in other words, excludes the researchers, not because it is in itself immoral to perform these experiments, but because it is in itself

immoral to perform these experiments, but because they cannot be relied on to perform the relevant theoretical and practical tasks involved in reasoning about their subjects' health needs, as confidently as nonparticipating physicians could be. Thus, when it comes to the secondary question of who should be legally permitted to perform these experiments, perhaps who should be called upon to decide who should be permitted - not whether it would be wrong to perform such experiments - then this exclusionary reason is in itself a moral reason. It is important to note that this secondary question, "Who should be allowed ... ?" is not itself a legal question, but a moral one. The parallel legal question would be, "Who is (by law) permitted ... ?"

(15) Utilitarian Reasoning. In another example in the same volume,³⁰ Dr. Francis D. Moore relates the story of how 250 years ago, a Dr. Zabdiel Bolston, encouraged by the Reverend Cotton Mather, conducted a research experiment without any preliminary animal experiments whatever. He inoculated persons with the virus of smallpox during a smallpox epidemic. The results: while the natural disease produced a 15 percent mortality, the individuals who received the inoculation suffered a 2 percent mortality. Dr. Moore does not comment directly on this case, but he appears to think that the risks were well worth taking, in view of the developments for which it paved the way. This is an argument based on utilitarian considerations. The benefits gained by future generations are thought to outweigh the harm and the risks undergone by those subjected to the experiment. Some utilitarian moralists would no doubt be inclined to treat this as a moral argument, but others who lean towards so-called rule-utilitarianism³¹ would

reject it. Be that as it may, that such a utilitarian is arguing morally would show itself in the way in which, if he accepts the principle that very great future gains justify present risks and losses, he is concerned to reduce these present risks to a minimum and to distribute them fairly.

(16) Political Reasoning. Suppose now that one of the discussants is a Congressman, and that he argues against a legislative proposal requiring all hospitals to set up Hospital Research Review Committees on which the general public is strongly represented, on the grounds that he would lose the next election if he supported such legislation, or that such legislation would never get through Congress even if he himself voted for it, or that if he succeeded in mobilizing enough support for this, he would in return have to give support to other measures he disapproved of. These would not be moral but political arguments, and they, too, would be technical arguments, as explained above.

NOTES

1. P.3: I do not here distinguish between 'ethical' and 'moral'. But I do distinguish between 'ethics' and 'morality'. Morality contrasts either with immorality or with law, religion, manners, and the like. Ethics does not have either of these opposites. A history of ethics is a history moral (or ethical) theory-- it is neither a history or morality from its emergence out of customs, nor a history of morals, what people thought right and wrong and the extent to which they lived up to their convictions.
2. G.E. Moore, Principia Ethica, Cambridge University Press.
3. W.D. Ross, The Right and the Good, Clarendon Press, 1930.
4. C.L. Stevenson, Ethics and Language, Yale University Press, 1930.
5. R.M. Hare, The Language of Morals, Oxford University Press, 1952; Freedom and Reason. Oxford University Press, 1965.
6. S.E. Toulmin, The Place of Reason in Ethics, Cambridge University Press, 1950.
7. See note 5.
8. On this topic the literature is extensive. I mention three widely read books: David P. Gauthier, Practical Reasoning, Clarendon Press, 1963. Roy Edgely, Reason in Theory and Practice, Hutchinson University Library, 1969, David A.J. Richards, A Theory of Reason for Action, Oxford University Press, 1971.
9. Patrick Nowell-Smith, Ethics, Penguin Books, 1954.
10. See for instance, C.H. Whitely, 'On Defining "Moral"', Analysis, 1959-60.
11. See e.g., D.W. Falk, 'Morality, Self, and Others', in Castaneda and Nakhnikian, ed. Morality and the Language of Conduct, Wayne State University Press, 1963.
12. See e.g., W.K. Frankena, 'The Concept of Morality', University of Colorado Studies, 1967.
13. See e.g., Alaskair MacIntyre, 'What Morality is not', Philosophy 1957; also C.H. Whitely, op. cit., and R.M. Hare, op. cit.
14. J.P. Sarte, Existentialism is a Humanism. Also R.H. Hare, op. cit., and 'Universalizability', Proc. Arist. Soc., 1954-5.
15. R.M. Hare, The Language of Morals, pp. 13 f. and 20 f.

16. Cf. W.K. Frankena, *op. cit.*
17. Cf. Philippa Foot, 'Morality as a System of Hypothetical Imperatives', Phil. Review, July 1972.
18. The sense of 'rational' as opposed to 'non-rational' is here irrelevant, since in this context, rationality in this sense is presupposed. We are not talking about animals which are non-rational beings, not even about fetuses which are merely potentially rational beings, but only about actually rational beings, those who already have the ability to engage in reasoning. What we are interested in is the distinction, within that class of beings, between those whose performance comes up to a certain standard and those whose performance falls below.
19. Such a view was probably held by C.L. Stevenson. See Ethics and Language. Also by David Falk, e.g., 'Action-guiding Reasons', Journal of Philosophy, Nov., 1973.
- 19a. See e.g., R. Duncan Luce and Howard Raiffa, Games and Decisions, John Wiley & Sons, 1965, pp. 94-97.
20. A brief discussion of these principles is contained in John Rawls, A Theory of Justice, pp. 408-416.
21. This is, of course, Hume's view or at any rate the view commonly attributed to Hume. Until recently, it was also the view commonly attributed to Aristotle. For a different view, see the recent work of John Cooper, Reason and Human Good in Aristotle, Harvard University Press, 1975.
22. Cf. Luce and Raiffa, *op. cit.*
23. See David Lyons, In the Interest of the Governed, Oxford University Press, 1973.
24. The case is taken from The Hastings Center Report, Vol. 5, No. 1, February, 1975, p. 49.
25. Such technical syllogisms must be distinguished from what is often called the Practical Syllogism, which are always first-person arguments and whose conclusion is the reasoner's action or his setting himself to act. An example would be: (i) I am set to cure this patient, (ii) If I am to cure this patient, I must insert a tube, (iii) So I am setting myself to insert a tube. We can ignore this form of reasoning since whether or not it is a valid form of reasoning it will occur as part of the performance of the practical task in all practical reasoning, and will not therefore help us distinguish moral from other kinds.
26. See, e.g., H.L.A. Hart, The Concept of Law, Clarendon Press, 1961, pp. 89-96.
27. See, e.g., Richard A. Wasserstrom, 'The Obligation to Obey the Law', University of California Los Angeles Law Review, Vol. 10, May, 1963. See also Hart, *op. cit.*, Chs. V, VIII, IX.

28. See e.g., John Austin, The Province of Jurisprudence Determined, Weidenfeld and Nicholson, 1954. Lecture V.
29. See J. Raz, 'Reasons for Action, Decisions and Norms,' Mind, Vol. LXXXIV, No. 336, Oct. 1975.
30. Third Academy Forum, Experiments and Research with Humans, pp. 16-19.
31. For an excellent if somewhat difficult discussion see David Lyons, The Forms and Limits of Utilitarianism. Clarendon Press, 1965. A brief historical survey of the main forms of utilitarianism are contained in Anthony Quinton, Utilitarian Ethics, Macmillan, 1973. A stimulating confrontation between a utilitarian and an antiutilitarian can be found in J.J.C. Smart and Bernard Williams, Utilitarianism, For and Against, Cambridge University Press, 1973.

DISTRIBUTIVE JUSTICE AND MORALLY RELEVANT DIFFERENCES

Tom Beauchamp, Ph.D.

I. The Concepts of Justice and Distributive Justice

The Meaning and Types of Justice. Sidgwick, Rawls, and others have argued forcefully that our basic notion of justice is more akin to the notion of fairness than to most any other moral notion. While they are right to insist on the close conceptual connections between these terms, perhaps the single word most closely linked to the general meaning of "justice" is "desert." One has acted justly towards a person when that person has been given what he is due or owed, and therefore has been given what he deserves and can legitimately claim. It may be that a person deserves to be awarded a prize, for example, in which case justice has been done when that person receives the prize. What persons deserve and hence can legitimately claim is based on certain relevant properties which they possess. Because a person possesses the property of being a law-breaker, or of otherwise wrongly treating others, we are justified in allocating an appropriate punishment. But it is wrong, as a matter of justice, to allocate a punishment or reward if the person does not possess the relevant property. It is wrong or unjust of a man to punish his dog for knocking a child down when in fact it was the man's negligence which led to the incident. Similarly, it is unjust to reward a superior for the work of his subordinates when it was not his guidance which led to rewardable productivity.

The expression "distributive justice" refers to the proper distribution of social benefits and burdens. Paying taxes and serving on juries are distributed burdens, while welfare checks and foundation grants are distributed benefits. Recent literature on distributive

justice has tended to focus on considerations of fair economic distribution, especially unjust distributions which occur in the form of inequalities of income between different classes of persons and unfair tax burdens on certain classes. But clearly there are many problems of distributive justice.

Comparative and Non-comparative Justice. It is also crucial to the idea of justice that deserts be comparative or comparable. Justice is said to be comparative when what one person deserves is measured by balancing the competing claims of other persons against his claims. Here the social condition of others affects how much an individual is due. Justice is non-comparative, in contrast, when desert is judged by a standard which is independent of the claims of others (e.g. an innocent man never deserves punishment). This paper deals exclusively with comparative justice.

Scarcity and Distributive Justice. It is noteworthy that distributive justice is a notion which applies only to the distribution of scarce benefits, where there is some competition for the benefits. If there are plenty of fish in a river for everyone to have as many as he can catch, we do not establish patterns of distribution. It is only when we are worried that the fish supply will be exhausted or that future fishermen will be unfairly affected by present fishing that we set limits to the number of fish they may catch. There are, of course, various schemes which could be devised for the distribution; but that is not the present point. The point is that there are no problems of distributive justice and no need of principles of distributive justice until some measure of scarcity exists. Even when burdens rather than benefits are being allocated, there is competition for the least disadvantageous distribution.

David Hume pointed out that we have developed the concept of justice in order to handle problems of conflicting interest when claims are being pressed by conflicting parties. As he put it, there would be no point to having rules of justice unless society were composed of persons of limited sympathy in the competition for scarce resources. The rules of justice serve to strike a balance between those conflicting interests and claims that repeatedly occur in society. This shows a close link between the lawful society and the just society, since law and morality are our explicit tools for balancing conflicting claims.¹ Nonetheless, the law may be unjust; and there may be many rules of justice which are not connected to the law or to legal enforcement. There seems to be no escape, then, from the conclusion that the notion of comparative justice presupposes parties with conflicting claims who attempt to justify their claims by appeal to basic moral rules.

Just Procedures and Just Results. There also exists an important distinction between just procedures and just results. The term "distribution" may refer to the process or procedure of distributing, or it may refer to the product or result of some system of distribution. Ideally, of course, it is preferable to have both just procedures and

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"Justice" is sometimes used as a virtual synonym of "lawful," and sometimes even of "good." Thus, it is often said that the just society is the lawful society or the good society. While it may be true that the just society is both lawful and good, it cannot plausibly be claimed that this characterization captures the meaning of "justice" very well.

just results, but it is not always possible to have both. For example, one might achieve a just result in distributing health care, but one might use an unjust procedure, such as illegal taxation of certain groups, in order to achieve it. One might also have a just procedure, e.g. a lay-professional interdisciplinary ethics committee in a hospital which selects patients for dialysis, and yet reach unjust results (since, say, certain information was not available or a member of the committee was prejudiced, etc.). In discussions of distributive justice it is often the system which is in question, and yet those who are criticizing the system may do so by pointing to unjust results. It is important to be clear, then, on whether it is the procedures or the results which are under consideration.

Formal and Material Principles of Justice. Justice in the sense of comparative desert has been analyzed in different ways in rival theories. But common to all theories of justice is a rather minimal principle which is traditionally attributed to Aristotle: equals ought to be treated equally and unequals unequally. This elementary principle is referred to as the principle of formal justice, or sometimes as the principle of formal equality. It is said to be formal because it states no particular respects in which equals ought to be treated the same. Effectively it says that no matter what respects are under consideration, if persons are equal in those respects, then they must be treated equally. More fully stated in negative form, the principle says that no person should be treated unequally, despite all differences with other persons, until such time as it has been shown that there is a difference between them relevant to the treatment at stake. In a more positive form, the

principle says that individuals who are equal in the relevant respects must be treated equally, while individuals who are unequal in the relevant respects should be treated differently in proportion to the differences.

The problem with the formal principle is notoriously more in its aloofness than in any deficiency of content. That equals ought to be treated equally, by law and elsewhere, is not likely to stir disagreement. But who is equal and who unequal? Presumably all citizens should have equal political rights, equal access to public services, and should receive equal treatment under the law. But almost all would allow that distinctions based on experience, deprivation, merit, and position do sometimes introduce criteria justifying differential treatment.

Any plausible theory of justice, then, must explain the respects in terms of which people should be equally treated, which involves specification of relevant properties. And it seems clear enough that not just any proposed criteria are morally fair. For example, if it is judged a good reason for not interviewing women for jobs that they make male interviewers nervous, then this introduces a proposed relevant difference. Yet this difference scarcely seems compatible with justice, since it allows a blatant injustice based on a morally irrelevant property. The really difficult questions about justice arise when we try to specify the relevant respects in terms of which people are to be treated equally. Any principles which so inform us are said to be principles of material justice, because they put material content into the theory. Examination of some major material principles of distributive justice is the next order of business.

II. Principles and Theories of Distributive Justice

In the philosophy of distributive justice there are a few widely discussed, and almost as widely accepted, material principles of distributive justice. Each principle mentions a relevant property on the basis of which burdens and benefits should be distributed. That is, each principle asserts a standard of relevance for purposes of distribution. The standard is normally, though not necessarily, a property which persons possess or fail to possess. What makes each principle a plausible candidate is the plausible relevance of the property it isolates. The following is a fairly standard list of the major candidates for the position of valid principles of distributive justice (though still different and longer lists have been proposed):

1. To each person an equal share
2. To each person according to individual need
3. To each person according to individual effort
4. To each person according to societal contribution
5. To each person according to merit (individual ability)

There is no a priori barrier to acceptance of more than one of these principles, and some theories of justice accept all five as valid. Most societies use several of them, applying different principles of distribution in different contexts. In the United States, for example, unemployment and welfare payments are distributed on the basis of need (and to some extent on the basis of previous length of employment); jobs and promotions are in many sectors awarded (distributed) on the basis of demonstrated achievement and merit; the higher incomes of wealthy professionals

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cf., e.g., Nicholas Rescher, Distributive Justice (Indianapolis: Bobbs-Merrill, 1966), Chapter 4.

are allowed (distributed) on the grounds of superior effort or merit or social contribution (or perhaps all three); and, at least theoretically, the opportunity for elementary and secondary education is distributed equally to all citizens.

Theories of distributive justice are commonly developed by emphasizing and elaborating one or more of the material principles of distributive justice, perhaps in conjunction with other moral principles. Thus, Egalitarian theories emphasize equality; Marxist theories emphasize need; Capitalist theories emphasize contribution and merit; Utilitarian theories emphasize a mixed use of such criteria so that public and private utility are maximized, etc. The viability of any such theory of justice is determined by the quality of its moral argument to the conclusion that some one or more selected material principles ought to be given priority (or perhaps even exclusive consideration) over the others.

Obviously consideration cannot here be given to the detailed nature either of principles or of theories of distributive justice. Nonetheless, it is important to see how from such meager and abstract beginnings as "the principle of _____" both relevant properties and public policies based on justice can be developed. Consider, as an example, the development of policies based on the principle of need. The principle of need declares that distribution is just when it is based on need. But how are we to understand the notion of a need? Certainly the term is subject to different interpretations, and one must settle on a meaning before proceeding further. In general, let us suppose, to say that a person needs something is to say that without it he will be harmed (or at least detrimentally affected). We can fill this basic idea out

by calling on the formal principle of justice, which requires us to say that people of equal need should be treated equally in regard to the satisfaction of these needs, while those who have unequal needs should be treated unequally. There are instructive examples of our acting on this principle which show its immediate relevance to contexts of distribution. In hospital wards people are given equal amounts of blood when they need equal amounts and unequal amounts when the amount needed is unequal. However, this analysis of needs does not take us far, since we are not required to distribute equally for all needs--such as needs for pets, athletic equipment, nightgowns, peaches, etc. (unless one is prepared to defend a radical form of egalitarianism). Presumably we are interested only in fundamental needs, so we ought to look further at this notion.

To say that someone has a "fundamental need" for something is to say that he will be harmed or detrimentally affected in a fundamental way if he does not have that thing. Examples of fundamental harms would be malnutrition, serious bodily injury, and the withholding of critical information. Without certain forms of food, health care, and education, these harms may befall us; hence we say we have a fundamental need for certain foods, health care facilities, and shelter. Generally these are needs which are necessary for survival, or more accurately for survival in a state of existence which is itself better than non-survival.

Now if one accepts a theory of distributive justice which permits appeal to the principle of need, then the more one refines the notion of needs, as we have done in preliminary fashion above, the closer one moves toward the relevant properties necessary for the formulation of

a public policy position. For example, if there exists a fundamental need for health care facilities, then it would have to be decided which needs are fundamental and which are not in order to develop a national health care policy. Anyone who had such needs would have the relevant properties. While this sort of theoretical refinement cannot be carried out here, it is of vital importance to notice the role of the first step in the argument--the acceptance of the principle of need as a valid material principle of justice. If one rejects rather than accepts the principle of need (while accepting, say, only contribution and merit), then one could judge such refinements inapplicable as a matter of justice and would be opposed in principle to the refinements and applications to public policy mentioned above. All public policies based on distributive justice derive ultimately from the acceptance of one or more material principles of distributive justice and from some procedure for refining them.

III. "Relevant" Respects and Classes of Subjects

The notion of relevant respects or relevant properties is a particularly vexatious one, and this section is devoted exclusively to its elucidation. I begin with a recapitulation of the previous two sections, as they have introduced the problem of relevant respects.

The formal principle of justice requires that individuals who are equal in the relevant respects be treated equally. Material principles of justice then specify what the relevant respects are, thereby excluding other respects as irrelevant to the treatment under consideration. A simple example is provided by a large company which offers free in-house legal services for employees. Suppose the company distributes

jobs on the basis of demonstrated ability, salaries on the basis of contribution, and free legal services on the basis of need. These three material principles fix relevant differences and also fix relevant similarities. Differences in pay, for example, are determined by differences in contribution (the relevant differences in this context), while similarities in pay are established by similarities in contribution (the relevant similarities). Obviously the same can be said about the allocation of jobs and legal services.

Moreover, further detailed specification of the criteria of ability (e.g., a certificate from a training school), of contribution (e.g., a salesman's total monthly sales), and of need (e.g., any legal service without which a person would be detrimentally affected) serves to fill out the precise nature of the relevant respects. These relevant respects can be correctly or incorrectly fixed. They are correctly fixed when supported by moral principles and incorrectly fixed when unsupported by moral principles (or when supported by incorrect "moral" principles), as we shall now see.

Established Relevance and Justified Relevance. However obvious the preceding may appear, there are theoretical difficulties in explicating the notion of relevant respects, as well as practical problems in the development of public policies. In some contexts relevant respects are firmly established, perhaps by tradition and perhaps by moral principle. Here it would be generally (though not always) inappropriate to challenge the established relevant respects by attempting to substitute others. For example, trophies are awarded (distributed) at the end of tennis tournaments on the basis of achievement; and how

achievement is to be determined is firmly set by the tradition-bound rules of tournament tennis. Similarly, as a moral matter, prison terms are not distributed to those who are not found guilty of crimes, since as a firm matter of law and morality, guilt is relevant to conviction.

However, in many controversial contexts it is morally appropriate either to institute a policy which establishes relevant respects where none has previously been very firmly established or to develop a new policy which revises standard or proposed "relevant" respects. If a person is chosen to be an ambassador to a foreign nation merely on the basis of wealth, party affiliation, and loyalty to the chief executive, it is arguably the case that these operative (and perhaps even traditionally entrenched) "relevant" properties are from the point of view of justice arbitrary and irrelevant. [Here it would be argued that: "You ought as a matter of justice to shift your operative set of 'relevant' properties to the right set of relevant properties, which would include linguistic facility, knowledge of the country, administrative experience, past contribution, etc."]

Similarly, if football scholarships to a university are awarded simply on the basis of ability as a football player and without reference to scholastic ability, it is arguably the case that the "irrelevant" property of scholastic ability ought as a matter of justice to be recognized as relevant. [Under the assumption that such resources are scarce and highly competitive, it would be argued here that: "You ought as a matter of justice to modify your operative set of 'relevant' properties to include scholastic ability."]

In these examples it is being argued that from the point of view of justice certain properties accepted as "relevant" are actually irrelevant

and that certain properties presumed "irrelevant" are actually relevant.

The Role of Argument and Decision. It is widely assumed that relevant properties are fixed independently of both moral argument and human decision, which establish them as either relevant or irrelevant. Just as the applicable rules determining the eventual winner of a tennis tournament are valid whether we know the rules or not, so we are tempted to think when some moral controversy arises that relevant properties are similarly fixed independently of human awareness of them. There is something almost certainly right, but something just as certainly misleading about this thesis. What is right is that basic principles of morality control the relevance and irrelevance of properties. If basic moral principles are not arbitrary and not changeable merely by individual human fiat (an assumption of moral philosophy which is here taken for granted), then the properties which such principles determine to be relevant are also neither arbitrary nor mere matters of individual preference. Any decision, then, will be one with attached moral constraints. This important point requires further explanation.

Consider the issue of experimentation on adult human subjects. How shall this burden be distributed? The formal principle of justice declares that we must treat everyone who is alike in the relevant respects. But which respects are here relevant? Suppose the members of one class of adult persons have consented to participation, are informed regarding the experiments and their risks, and have not been coerced in giving their consent. Suppose, however, that the members of another class of persons either have not consented, or are not informed, or have been coerced. We would all agree that consent, understanding, and non-coercion are clear cases of non-arbitrary relevant differences (whether or not

these properties are sufficient conditions of justified experimentation). But why are these respects relevant, while properties such as tallness, handsomeness, and I.Q. are not relevant? The answer is that their relevance is non-arbitrarily fixed by moral principles. Non-coerced, informed consent is relevant because basic moral principles such as respect for persons and human autonomy determine relevance. Stated negatively, if consent, understanding, and non-coercion were not present, then (coerced) experimentation would violate basic moral principles protective of human autonomy and respect for persons. No parallel moral constraints require consideration of tallness, handsomeness, and I.Q. This also explains why we often use the language of morally relevant properties and morally irrelevant properties.

We insist that the choice of such properties is not morally arbitrary or merely a matter of subjective preference, precisely because their selection is backed by moral principles.

On the other hand, there are occasions where moral principles do not in any clear fashion determine relevant properties. Usually this occurs not because moral considerations are unimportant, but rather because there are conflicting moral demands where no single moral principle is determinative. In such cases a moral decision concerning the weight of competing moral claims is required, and this decision in turn fixes the acceptable relevant properties. Whether members of minority groups formerly discriminated against should be given preferential consideration in hiring is one such issue with important policy implications. Whether 18-year olds should be allowed to vote is another. A particularly striking example is found in the current controversy whether a transsexual

female should be allowed to compete in women's tennis tournaments. Presumably the only relevant property governing qualification for such a tournament (assuming the requisite tennis ability) is that of being a woman. However, possession of the property of transsexuality in this context seems to throw into open question what the appropriate criteria are for being a woman. We are then invited to consider whether chromosome structure is relevant or irrelevant. This issue at first appears to be either an empirical or a conceptual dispute concerning necessary and sufficient conditions of being a woman. More plausibly, it is a moral problem of justice. On the one hand, the question is whether it is fair to non-transsexual women to allow transsexuals to compete; and, on the other hand, it is asked whether it is fair to transsexuals that they be excluded. Such an issue will almost surely be decided primarily on a moral rather than a conceptual basis. It will be decided by considering the weight of moral arguments on each side, and in the end the relevance or irrelevance of chromosome structure and of other proposed criteria will be decided by reference to moral standards of fairness.

A great many moral problems and public policy decisions take precisely this dilemmatic form. There are powerful moral reasons in such cases for accepting two or more sets of different and competing properties as equally relevant, even though only one can be adopted and put in service. It would be convenient if relevant properties were always fixed in the way tennis rules and criteria of informed consent are fixed, but often they are not settled in these ways and must be explicitly fixed by moral deliberation and decision. Usually in such cases it is neither unreasonable

nor unfair if the final decision favors either of two or more competing positions.

Classes of Subjects. Classes of subjects which are the objects of moral concern should be grouped for ethical purposes only by the relevant properties which they share in common, though there is often a temptation to group them in terms of convenient but irrelevant properties. Suppose a statute governing jury duty excuses all men but excuses no women, on grounds that there are many more men in the working population than women. Here justice requires us to say that an undue burden is placed on women and an undeserved privilege is granted to men. Being male or female is irrelevant, and so is the sexual grouping. If the relevant property excusing jury duty is employment, then employed men and employed women should be excused without regard to sex.

Or consider again the complicated matter of human experimentation, in this case with special reference to prisoners. For simplicity suppose there are two and only two classes of prisoners: (1) those whose restrictive environments are as non-coercive as normal non-prison environments and (2) those whose restrictive environments are inherently coercive. Suppose further that laws governing experimentation allow voluntary submission to experimentation by non-prisoners but exclude all prisoners on grounds that prisons are coercive environments which preclude voluntary consent. Such a law would be based on a false belief which caused it to discriminate arbitrarily against class (1) prisoners. The law has mistakenly used the irrelevant property of being a prisoner rather than the relevant one of being in an inherently coercive environment. Moreover, the mistake would be compounded if the members of other inherently

coercive environments (e.g. military training camps, asylums for the mentally infirm, etc.) were not similarly excluded. In general, rules and laws are unjust when they make distinctions between classes that are actually similar in what is actually a relevant respect, and/or fail to make distinctions between classes that are actually different in what is actually a relevant respect. This is a simple but important policy application of the formal principle of justice.

IV. The Principle of Fair Opportunity

Material principles of distributive justice which state relevant properties of proper distribution have until this point occupied the bulk of our attention. Consider now those properties which might and often do serve as bases of distribution but which in virtually all contexts are not relevant to distribution, or at least should not as a matter of justice be considered relevant grounds. I am thinking of such characteristics as sex, race, religion, I.Q., and social status. We do in some limited contexts use such properties as relevant--e.g., if a script calls for an actor in a male role, then females are excluded. Still, we do not allow distribution of economic considerations solely or even primarily on the basis of such properties. (Acting ability is the primary property in the actor example.)

It is important to ask why we do not accept principles such as "to each according to sex" or "to each according to I.Q.," as valid principles of distributive justice. The most widely accepted reason why we exclude such properties, and indeed regard them as discriminatory, is because to use such principles would be "to treat people differently

in ways that profoundly affect their lives because of differences for which they have no responsibility."³ This reason for excluding the use of distributive principles in some contexts has important implications, for this understanding of justice effectively means that differences between persons can fairly be made relevant differences only if those persons can be held responsible for these differences.

To see the importance of this point, consider the distribution of benefits in a state. The fair opportunity principle, as I shall call it, says that none should be granted benefits on the basis of their (let us say "advantageous") properties when they are not responsible for those properties, and it also says that none should be denied benefits on the basis of their (let us say "disadvantageous") properties when they are not responsible for those properties. Such properties are never grounds for morally acceptable discrimination between persons based on justice because they are not the sorts of properties that one has a fair chance to acquire or overcome. Of course in many societies properties such as religion and social status may not be acquired, and can be "overcome." I am thinking primarily of race, sex, and I.Q.-- those properties that seem to bedevil fair treatment more than any others known to the human race. But however that may be, the fair opportunity principle is probably best treated as a second-level principle of distributive justice.

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W. K. Frankena, "Some Beliefs about Justice," The Lindley Lecture, as quoted in Joel Feinberg, Social Philosophy (Englewood Cliffs, N.J.: Prentice-Hall, 1973), p. 108 (*italics added*).

Consider in this connection how the fair opportunity principle could be used in direct application to problems of the institutionalized mentally infirm. If IQ is something for which a person is indeed not responsible, and if none should be denied the benefits of the state (or other distributional system) on the basis of any such property, then it would be unjust not to distribute to them the benefits generally conferred upon all who share in the system of benefits. But this is still somewhat vague and in need of theoretical amplification. Consider the specific example of a basic education. We confer this benefit on all citizens equally, and we would consider a person deprived or harmed if he were unable to receive it. Suppose that in a given community an efficient school system is maintained which gives a uniform opportunity for a high quality education to all, regardless of sex, race, religion, etc. Such a system, however, will not confer an education upon those students with reading difficulties or mental deficiencies. They require special training in order to overcome their problems and to receive what for them is a minimally adequate education. If such persons were responsible for their slowness, we might say that they deserve no special training and simply have to expend more effort. But it is precisely when we discover that they are not responsible that we say they deserve special consideration; and hence we introduce different kinds of education for different kinds of students regardless of the differential in cost (within limits, of course).

Notice that it is not the economic consideration of an equal distribution of resources which is being proposed. We do not say that IMI's (or slow learners with special reading problems, etc.) should get the same amount of money or training or resources as other pupils because they

are not responsible for their condition. Rather, we say they should get what for them is a quality education, even if it costs more, because the principle of fair opportunity requires that they receive it. Any other system of distribution would lead to the consequence that an undue burden is being placed on this class of persons. The burden is undue because placed in violation of a principle of justice.

The argument just presented is a sketch of a justification of unequal distribution to the institutionalized mentally infirm which is based on the (second-level) principle of justice which I have called fair opportunity. The argument has been that you cannot introduce criteria such as effort and merit in cases where a person is handicapped through no fault of his own. Determining a person's due or desert exclusively on the basis of such principles would in fact be morally wrong; for, as applied to the handicapped, such principles do not satisfy the requirements of the principle of fair opportunity. It is not my intent to actually defend an unequal distribution of resources to IMI's. I have used this argument merely as an example of the implications which principles of justice have for problems of public policy.

This paper discusses various problems of distributive justice, with emphasis on the major distinctions, principles, and methods of moral argument which are shared by most who have written on the subject. No attempt is made to develop the "right" theory of distributive justice, but a definite framework for understanding the wider implications of any particular theory of justice is provided. The paper deals in order with the following topics:

- I. The Concepts of Justice and Distributive Justice
- II. Principles and Theories of Distributive Justice
- III. "Relevant" Respects and Classes of Subjects
- IV. The Principle of Fair Opportunity

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THE IDENTIFICATION OF ETHICAL PRINCIPLES

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The Identification of Ethical Principles

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Congress has charged the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research "to conduct a comprehensive investigation and study to identify the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects." This paper focuses on one part of that charge--the identification of ethical principles--and analyzes some of the issues raised by attempts to classify some considerations, reasons, arguments, etc. as "ethical" or "moral" and in distinguishing them from others such as political, legal, and theological. While indicating some of the major options regarding these issues in contemporary ethics, I shall develop my analysis with special attention to policy-making and draw examples from that activity.

I. Setting of the Question

As a preliminary matter, it is important to inquire into the presuppositions of the question "how to identify ethical considerations or action-guides," and to suggest exactly how I shall approach it and attempt to avoid certain pitfalls.¹ Perhaps Congress attached little or no significance to "ethical" as a modifier of "principles," as it may have been interested in what ought to be done without worrying too much about the sorts of reasons that could be invoked. On the other hand, assuming that Congress attached some importance to "ethical," one should try to determine what sorts of principles would be thereby excluded from considerations and how "ethical" ones are distinguished from and related to them.

But why would one be interested in distinguishing sorts of considerations instead of dealing with the substantive arguments for policies however they might be classified? Why not ask whether there are good reasons for a policy without worrying about whether those reasons can be classified as ethical, or legal, or

political, or theological? Interest in the question presupposes a certain historical and social context marked by what Talcott Parsons and others have called "differentiation."² The western world in particular has been altered by a process of differentiation which rendered activities and institutions distinct and functionally specific. Thus, one can see how politics, law, economics, and religion, for examples, have become differentiated from each other; they no longer reside comfortably under a "sacred canopy." Functional rationality came to legitimate the norms in various institutional areas such as politics and economics. This process of differentiation was also a process of secularization in one sense as "autonomous institutional 'ideologies' replaced, within their own domain, an overarching and transcendent universe of norms."³ In another sort of world, with less pronounced differentiation, questions about the classification of considerations for policies would appear to be less important. In such a world agreement about the relevance of certain considerations (such as religious ones) for policies could be assumed even when there was dispute about the substance.

Our interest in the classification of reasons may well reflect a belief that certain considerations are not relevant to public policy. Although we are interested in the terms of public debate in a pluralistic society, we must be wary of supposing that classifications of reasons can finally prove conclusive in substantive debate--a supposition that may motivate some of the interest in this question. To distinguish "moral" or "ethical" considerations from other sorts (which we will label "nonmoral") is not to determine how much weight those sorts of reasons should have unless one writes certain inappropriate evaluations into the definitions of "moral" or "ethical."⁴ Thus, we shall be wary of "ideological" definitions that write a substantive moral conclusion into the distinction between moral and nonmoral considerations. The distinction between "moral" and "nonmoral" should not be confused with the distinction between "moral" and "immoral." The

former is a "second-order" distinction, and the task of analyzing it is often labelled metaethics in contrast to normative ethics. Although the distinction between metaethics and normative ethics is controversial (and some suggest that some metaethical views imply normative ethical ones), I am interested in what conditions must be met for a position or argument to be considered moral rather than nonmoral. I won't deal with the criteria of "good" and "bad" moral reasons.

Attempts to distinguish moral and nonmoral reasons may be primarily reportive or reformative. A reportive definition describes and elucidates contemporary usage, while a reformative approach proposes a particular way of distinguishing "moral" and "nonmoral" even if it modifies ordinary usage. Working descriptively, a philosopher might ask what our ordinary concept of morality is or entails, "what we actually mean by 'moral' and 'morality' in their relevant uses, or what the prevailing rules are for the use of these terms."⁵ The reformative approach would also draw on contemporary usage, but it would not be bound by it.

Most philosophical discussions of "morality" appear to be reformative or revisionist in intention, even when they are not so acknowledged, and I too will be most interested in recommendations about how we should use the terms. People make such recommendations in specific contexts and for definite purposes. Why do we want to distinguish moral and nonmoral action-guides? A moral philosopher might be interested in expanding or contracting the scope of his legitimate endeavors; for instance, a moral philosopher may think that it is appropriate to discuss "personal ideals" and he may argue that a definition of morality must be broad enough to encompass them.⁶ What such a philosopher considers in defining morality is certainly relevant to the policy-maker who is also interested in the classification of arguments. 'But why one wants or needs a definition of morality is not irrelevant to determining the sort of definition that is appropriate.

Even for a revisionary definition of morality, proposed for some fairly specific purposes and judged by its usefulness particularly in illuminating certain issues, ordinary usage remains an important but not decisive test. The proposed rules for using the terms should bear some close relation to ordinary usage, or substitution of terms would seem wiser. But contemporary usage is diverse and perhaps even imprecise and inconsistent. Joel Feinberg comments that "[t]he word 'moral,' reflecting a variety of disparate and contrary uses in the technical literature of law, theology, and philosophy, is not simply ambiguous, but ambiguous in such an extraordinary way that some of its senses are antonyms." His point holds for ordinary usage and not merely for technical literature. He also gives several examples,

On the one hand... 'moral' has the ring of supreme authority, and on the other, it still carries its original sense of informal 'customs' or 'ways.' Aristotle contrasted the moral with the intellectual; Kant identified it with the rational. Lawyers use it to refer, on the one hand, to loose and informal arrangements beneath the official attention of the law and, on the other hand, to an ultimate standard for appraising the law.⁷

Furthermore, as I shall emphasize later, "moral" sometimes refers to decisions and acts that should be left to individuals or small groups, because they are not sufficiently important to warrant the community's interference, and sometimes it refers to the issues that are considered so important to the community that it expresses certain judgments through laws and policies. This particular ambiguity is closely connected with the main options in the debate about the formal and material criteria of "moral" over against "nonmoral."

These ambiguities in contemporary technical and ordinary usage suggest that attempts to delineate the necessary and sufficient conditions may be doomed to failure. At the end of a search for those conditions for identifying reasons, considerations, and action-guides as "moral" in contrast to "nonmoral,"

one may simply have to conclude that "moral" and "morality" are "family-resemblance" words (Wittgenstein's phrase). They may be so open-textured that necessary and sufficient conditions cannot be identified. Nevertheless, an examination of some recent philosophical efforts to identify necessary and sufficient conditions of "morality" will be instructive.

II. Formal and Material Conditions of Morality

W. D. Hudson, a philosopher, offers the Parliamentary debate on the Divorce Reform Bill in 1969 as one example of first-order moral discourse in which policymakers try to determine what they ought to do (we could easily recall or imagine others regarding abortion and euthanasia as well as research involving human subjects):

This bill recognized the breakdown of marriage as the sole ground for divorce....The moral question which arises is: ought divorce to be reformed along these lines? That was the question debated at the all-night sitting....We may safely take this debate as an example of moral discourse. The participants put forward what purported to be their own answers to a moral question. They supported these with what they considered reasons appropriate to the settlement of a moral issue.

Hudson makes numerous assumptions about this debate in terms of its characterization as moral, and they may well be warranted, but whether other interpreters would also view the debate as involving "moral question" and as "an example of moral discourse" depends on their conceptions of "moral" and "morality." To ask "what ought we to do?", "what law or policy ought we to have?", or to judge "that proposed policy is wrong," may be to ask a moral question or to make a moral judgment. Clearly the judgment, for instance, is normative, but there may be many normative judgments and action-guides (such as etiquette) that are nonmoral. Our question is not which morality counts and how much it counts but what counts as morality.

Recent philosophers have held that one or more of several criteria determine what will count as a morality or moral action-guide. The main criteria are that

an action-guide must be (1) prescriptive, (2) universalizable, (3) overriding, and (4) indicative of a material content, particularly one that relates to effects on others. ⁹ Few philosophers quarrel with some notion of prescriptivity, except as it is filtered through the other formal features of universalizability and overridingness, and I shall thus emphasize 2 and 3. 1-3 are formal criteria that are taken to apply to any moral action-guide regardless of its content. Not what is held, but how it is held determines whether it is moral or not. 4, on the other hand, requires certain material content before the action-guide can qualify as moral. The formal criteria, taken singly or jointly, will, of course, admit a broader or wider range of judgments, as far as content is concerned, whereas #4 recognizes as moral only those action-guides, etc., that take account of some specified content. ¹⁰ Particular philosophers may, of course, claim that one or more of these conditions are necessary but not sufficient, necessary and sufficient, or sufficient but not necessary for applying the term "moral" to action-guide.

Consider the following arguments between government X and opponents of a war that X is undertaking. Government X claims that the war is just and that a policy of conscription is also just; its claims meet both formal and material criteria of morality. Among the opponents and resisters are

- A contends that the war is wrong (but his judgment satisfies only formal criteria of "morality").
- B contends that the war is wrong (but his judgment satisfies only the social material criterion of "morality").
- C contends that the war is wrong (and his judgment satisfies both the formal and social material criteria of "morality").
- D refuses to serve because military life with its hierarchy and its emphasis on obedience is incompatible with his ideal of human excellence.
- E doesn't want to risk being killed,

- F₁ insists that the war is not in the national interest and refuses to serve in it.
- F₂ condemns the war because the evil results will outweigh the good ones.
- F₃ argues that the war can't be won.
- F₄ claims that the war has not been authorized by the proper political authorities (cf. G).
- G holds that the war is illegal and unconstitutional (cf. F₄).
- H says that only one war can be just--the battle of Armegeddon which God will command and direct.

I choose this case as a focal point because we have all heard (and perhaps made) many of the above arguments in the last several years and because we probably also have some rough idea how we would classify them--moral, prudential, political, legal, religious, etc.

With this case in mind, let us turn to a more detailed discussion of formal and material conditions of morality. Among the formal conditions I shall emphasize universalizability and supremacy or "overridingness." Hare and many others construe universalizability as a logical requirement, not a substantive moral one: to call a judgment universalizable means "only that it logically commits the speaker to making a similar judgement about anything which is either exactly like the subject of the original judgment or like it in the relevant respects. The relevant respects are those which formed the grounds of the original judgements."¹¹ We cannot make different moral judgments about acts that we consider to be exactly or relevantly similar. One might base this thesis on the logic of "moral" or "oughts" or judgments generally (including both evaluative or normative and descriptive judgments). Universalizability does not distinguish moral judgments from other sorts although it may be a necessary condition for any normative judgment. Hare apparently thinks that universalizability together with prescriptivity and perhaps supremacy are sufficient as well as necessary for moral judgments and action-guides.

The formal approach has been criticized on several grounds. First, it casts its net so widely that it catches numerous action-guides that we ordinarily consider to be nonmoral. In particular, the criterion of supremacy, overridingness, or superordination has a paradoxical effect. Hare contends that in one sense of "moral" ("perhaps the most important one"), a "man's moral principles...are those which, in the end, he accepts to guide his life by, even if this involves breaches of subordinate principles such as those of aesthetics or etiquette."¹² Although Hare appears to be working with a fairly clear distinction between moral and at least some nonmoral value judgments (such as aesthetics), both share universalizability and prescriptivity and so could only be distinguished by the supremacy of the moral judgment. It is difficult to see how the formalist can avoid the odd consequence that if someone holds aesthetic judgments as supreme, as overriding all other judgments, he must have taken aesthetic judgments as his moral ones. Whatever action-guides a person takes to be supremely authoritative or as his way of life would appear to constitute his morality. For instance, a biomedical researcher whose life is devoted to scientific progress could conceivably be said to have scientific progress as his morality. While there is some warrant for such a view in ordinary usage, it obfuscates some of the usual distinctions between religion and morality and, perhaps, would permit even a thoroughgoing, serious prudentialism to be considered moral (as contrasted to nonmoral) if its proponents took it as supreme and overriding and if it met the other formal conditions of morality.

The criterion of supremacy of "overridingness" at least in its absolute sense appears to gloss over a significant human problem (to call it a "moral" problem at this point would beg questions) in that it prejudges the dominance of particular sorts of action-guides or reasons. Much of our serious debate concerns which sorts of considerations should be given the most weight, for

instance, prudential or moral ones. Thus the debate about whether a position is moral is simultaneously a debate about how much weight and significance it should have, but the formalist won't let the content determine whether the position is moral. As Hare says, "there is absolutely no content for a moral prescription that is ruled out by logic or by the definition of terms."¹³

This feature of "overridingness" (or other terms such as ultimacy, supreme authoritativeness, and finality) appears to rule out another fundamental human question: "why be moral?" For if, by definition, a morality or moral action-guide is supremely authoritative, it makes no sense to ask "why should I/we abide by it?"¹⁴

The use of the formal criteria, particularly universalizability, has been criticized as hopelessly "culture-bound," "ethnocentric," and even "excessively Protestant" and "individualistic." Most of the charges hold that universalizability cannot be construed merely as a "logical" thesis, for it actually builds in a particular morality. It pretends to be neutral, but it actually chooses sides within morality, hiding its allegiance to "liberal morality" under the guise of neutral, logical analysis.¹⁵ The requirement of universalizability fails to take account of radical moral disagreement (e.g. whether to take the standpoint of impersonality). It sets the terms of moral debate and the weight of sorts of considerations without taking responsibility for doing so. Although I share this concern of many critics of the universalizability requirement, I am not convinced that the requirement must be surrendered. It is clearly not sufficient, but it does appear to be a necessary condition of moral judgments. It begs fewer questions if we clearly separate it from the condition of supremacy.

One advantage that could be claimed for the formalist understanding of morality is that a number of social conflicts whose participants offer prescriptive, universalizable, and overriding judgments can be construed as moral. Thus, Hare describes a debate between a Nazi and a liberal as a moral conflict.

Nevertheless, it does not seem to be necessary to concede that both (or all) sides in a debate are offering moral considerations (as contrasted to nonmoral ones) in order to view the debate as a moral one; this point would seem to apply to the Parliamentary debate about the Divorce Reform Bill that I mentioned at the beginning of this section. A debate may be classified as moral because it is, in part, a debate about whether to be moral and to take the perspective of morality, or because it is a debate between a recognizable moral position and a nonmoral one (such as self-interest), as we do not hesitate to consider the personal conflict between duty and interest a moral one. When we classify as moral a debate between government X which claims that it is engaged in a just war and its opponents who hold that the war is wrong, we do not necessarily ascribe a "moral" claim to both parties.

The formal criteria of morality, as we have seen, appear to allow us to count as moral a wide range of judgments and action-guides, including some that would ordinarily be thought of as nonmoral. Several philosophers have proposed a narrower concept of morality that has some support in ordinary speech. It is both social and material. It focuses on regard or consideration for others, particularly for their welfare. Of course, some of the formal conditions such as universalizability involve some sociality (in so far as they insist on treating similar cases in a similar way or legislating for others), but the narrower concept of morality writes in "other-regardingness" or consideration of others. Furthermore, this narrower concept is material as well as social as it builds in regard for the effects on others' welfare. It characterizes morality by its "subject-matter," "its content, what it is about, the range or type or considerations on which it is founded." From this perspective, formal conditions may be necessary but they cannot be sufficient; a moral judgment or action-guide must also meet a material condition.

As in the discussion of the formal conditions I will only be able to deal with a few salient points about the social material condition. Furthermore, particular versions of this condition (just as particular versions of the formal conditions) may escape some of the objections which I try to state in general terms.

One major difference among the versions is the degree of specificity of effects on others' welfare. If one can be fairly specific about those effects and about welfare, obviously one can draw sharper boundaries between "moral" and "nonmoral." G. J. Warnock contends that the notion of "the welfare of human beings surely has...a perfectly clear and determinate core of centre," even while it also has "an extensive penumbral fringe of vagueness and indeterminacy." One can say that torture, starvation and humiliation are bad as a matter of fact, not opinion; likewise, one can say that love and care are better than hatred or neglect. Rejecting such criteria as happiness, others identify welfare interests as those associated with survival, security, health, etc.

Although he refuses to offer any specific content to the effects on others that must be considered, Frankena adds a clause that requires explication. He says that for an action-guide to be moral it must include judgments, rules, etc. that "concern the relations of one individual...to others" and "involve or call for a consideration of the effects of his actions on others (not necessarily all others), not from the point of view of his own interests or aesthetic enjoyments, but from their own point of view." Functionally, this requirement of consideration from the other's point of view is similar to the notion of a determinate core of welfare, which it is presumed the other would accept. Frankena's requirement rules out egoism or prudentialism if these are understood as basic perspectives (instead of being derived from a conviction that the welfare of others could best be protected by each person's pursuit of his own interests). Egoism or prudentialism could be a "working criterion" of morality but not its

basic principle. This social material condition, as sketched by Frankena, "rules out as non-moral only such AGs as pure egoism or prudentialism, pure aestheticism, and pure religion."²¹

A number of objections to making the social material condition necessary hold that it builds a substantive moral position into the definition of morality. The charge that this criterion builds in "utilitarianism", for example, may be more devastating for some specific statements of the content of human welfare than for more general statements, which leave open what effects on others must be considered and whether deontological considerations are germane.²²

The social material condition, at least on some interpretations, does not rule out particularistic moralities, for it does not require that effects on all others be considered, or that all others be counted as humans, but only that the effects on the welfare of at least some others be considered. Thus, it does not exclude the Nazi from the moral camp, for an argument on behalf of acts and policies that inflict suffering on some for the sake of others still qualifies as "moral" (in contrast to "nonmoral") although we may insist that the acts and policies are morally unjustified. Thus, if someone recommends a policy of massive, high-risk, non-therapeutic experimentation on prisoners on behalf of future generations, however much we may morally condemn that recommendation, we cannot dismiss it as nonmoral on the social material condition of morality. Indeed, it refers to a determinate core of welfare (the health of future generations) and it includes the effects on some others from their own point of view (what future generations need--not merely want). Considerable moral disagreement remains because of the necessary balancing or weighing of the welfare of one group against risks to another, the welfare of present vs. statistical lives, immediate vs. remote harms and goods, etc.

Although I am more interested in highlighting several issues than in defending a particular interpretation, I think that a strong case can be made that formal conditions of prescriptivity and universalizability and the social

material condition of "other-regardingness" are necessary and sufficient for moral judgments and action-guides. Because it is necessary to leave open for debate whether we should abide by moral or nonmoral action-guides, particularly when they come into conflict, I would omit the formal condition of finality, supreme importance, or ultimate authoritativeness. Only by emphasizing that human discourse remains open, even if the term "moral" is restricted by the above criteria, can one partially blunt the charge that one is making logical or conceptual analysis do the work of normative ethics or choosing sides in a moral debate while claiming to be neutral.

III. Ideals

Resister D presents his reasons by depicting his ideals. Although some ideals (for example, charity) may be otherregarding, D's ideal is not. It is an ideal of human excellence that makes no reference to the welfare of others; he simply doesn't want to be a subordinate in a military organization although he is not upset about killing in war or fighting in a putatively unjust war. His argument is similar to aesthetic ones and he might claim that participation in a military organization is "degrading." According to the social material criterion, his ideal is nonmoral, while according to the formal criteria, it could be moral.

Numerous factors that are not universalizable, etc., shape personal and institutional decisions, but I am only interested in those factors that can be invoked as reasons for decisions. The question is what form and content those reasons must have to count as moral and where ideals fall. Strawson has distinguished the regions of the "moral" and the "ethical," including social duties among the former and ideals among the latter, but this distinction which has little or no support in ordinary usage is unhelpful. From the standpoint of moral discourse, what are we to do with ideals? Do ideals constitute a level within morality or beyond it? What difference does it make whether we characterize them as moral or nonmoral?

Hare would consider D's reasons for his act as moral largely on the grounds that people do not hesitate to call such reasons moral, that moral philosophy should deal with them, and that ideals may be universalizable, prescriptive, and overriding. Their role in conduct, judgments, and justification is analogous to the role of moral principles. Others might say that ideals (as well as other "personal oughts") are at least similar to and akin to moral oughts. Although Frankena, on the other hand, is inclined to view non-otherregarding ideals as nonmoral, he thinks that they can be a legitimate subject of moral philosophy which must consider, for instance, whether such ideals have priority over moral principles in cases of conflict. Here again because the discussion in philosophical literature is partly concerned with the appropriate scope and subject matter of moral philosophy, some of the points may not be important to the policy-maker who is interested in the classification of arguments for somewhat different reasons. 25

One option is tempting but ultimately unsatisfactory. One might say, for instance, that a debate between observers (perhaps a clemency board) about whether D acted wrongly, should be pardoned, etc. would be moral because D's act has direct and indirect effects on others whether he recognizes and considers them. 26 Thus, these observers would be making moral judgments if they considered these effects on others or if they decided how much weight to give to government X's moral judgments (assuming their validity) in relation to D's nonmoral judgments. These observers could well be engaged in moral debate over a moral issue. But such a move would not deal with the question from the agent's standpoint--whether D is making a moral argument whatever he calls it. What is at issue is whether D supposes that the pursuit of his ideal relates to human welfare.²⁷ If we assume that the ideal does not involve otherregardingness and thus is purely personal, the argument between D and X could still be considered moral, for it concerns whether to be moral and whether X's moral reasons should take precedence over D's personal ideals.

One last point about ideals before turning to prudential and political judgments. Social ideals are often invoked in political debate. Most often they

have some reference not only to society (by definition) but also to effects on members. Nevertheless, there may be a social ethos that stresses the universal participation of all its citizens in military or alternative service or non-therapeutic research for quasi-aesthetic rather than moral reasons. The community might ask "what ought we to do?" but answer it with an answer to another question "who are we?" It will not do, I think, for an observer to say "that's obviously a moral issue, since following that ideal has effects on the welfare of others," For the representatives of the society may see it as a matter of ideals apart from those effects, and may be concerned with realizing those ideals or with expressing them in policies. Particularly in the language of expressing ideals, one finds an emphasis on policies that symbolize the community's ethos. For instance, in the recent debate over amnesty, many policy-makers and citizens asked what particular policies would symbolize about the nation: that it is vindictive or respectful of law and order, that it is forgiving or soft? Although the same policy may be justified by the same people in terms of a country's ideals and its moral standards (including the social material condition), and although both reasons usually appear together and are often hopelessly intertwined, the language of "public ideals" needs more attention. Such ideals bear some close kinship to morality, even when they don't meet the social material criterion, and they frequently present at least "semimoral" oughts.

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IV, Prudence

Objector E opposes and refuses to serve in the war because of his prudential calculation of risks to himself. He may take his egoism as overriding, prescriptive, and universalizable, and, if so, his position is "moral" according to formal criteria, at least according to some interpretations. On the other hand, he may not be basically egoistic, but rather derive his working egoism from a more basic principle that the general human welfare would be served by egoistic actions or that the world would be better off if everyone acted as he did. The latter version of his position

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would qualify as moral on some interpretations of the social material condition as well. Furthermore, even Frankena includes some duties to oneself under morality although it is not clear whether he claims that a system of morality must have some action-guides that are at least in part otherregarding or that each action-guide, to be moral, must be at least in part otherregarding.

But suppose that E is basically prudential and egoistic--he only wants to save his own skin. The issue between government X and E could still be construed as moral in the sense of being a debate about whether to be moral and about what weight morality should have on the scale of reasons for action. But E's own position would not be considered moral, for, as those who have insisted on the condition of otherregardingness contend,

'the moral point of view' involves, precisely and essentially, the abandonment of pure prudential egoism, and a readiness to consider as justifying grounds of action the interests or 'wants', ideally of everyone, but at any rate of at least some persons other than oneself.

A few more comments about prudence are in order. Traditionally (for instance, in Greek thought and St. Thomas Aquinas), "prudence" lacked the negative connotations it has since acquired. It had a different ring: "the pre-eminence of prudence... finally...signifies the directing of volition and action toward objective reality. The good is prudent beforehand; but that is prudent which is in keeping with reality....The immediate criterion for concrete ethical action is solely the im-³²perative of prudence in the person who has the decision to make." The radical change in the value of prudence resulted from the radical alteration in the understanding of reality, of the self and its world. For Machiavelli (The Prince, XXI), "(p)rudence consists in being able to assess the nature of a particular threat and³³ in accepting the lesser evil."

There are many precepts of self-protection, of which prudence is only one. If a person refuses to participate in a perilous experiment, he may be acting

prudently in the sense of taking few or no risks. "To act prudently is to play safe, for near-certain gains at small risks." But the precept of not wasting one's abilities is sterner than the precept of prudence. Furthermore, the prudent cannot be equated with the expedient. It may be prudent to save, but it may not be expedient to begin now; "reasons of expedience are reasons of a special sort: reasons for doing something on the ground that it is incidentally at hand to serve one's purpose, or because it serves a purpose quite incidental to the purpose for which we would normally be doing this thing,"³⁴

Falk contends that "personal oughts" such as prudence "all seem at least akin to a 'moral' ought in their action-guiding force and function," but he is hesitant to speak of them as more than "semimoral." "Oughts" that concern the interests of others seem to have a more stringent obligatoriness, partly because of their end and partly because, as Kant emphasized, an ought predicated on the assumption that one is pursuing an end (such as one's health) is at best hypothetical: "if (or as) you want to be healthy, you ought to get enough sleep, eat the right foods, etc."

Falk's main contention is sound: if we define "moral" to include a social material element, we might by formal criteria still consider some personal oughts such as prudence "akin" to "moral" or even as "semimoral." However we define "moral," we should not conclude that "personal oughts" are always inferior and subordinate to "moral oughts." That should not be a matter of definition. I think that little is gained by calling basically egoistic positions moral instead of nonmoral, as long as we recognize that this classification does not determine their weight and leave open for debate the sort of perspective we ought to adopt.

Furthermore, there is a form¹ of "social prudence" that involves calculations about the good for a larger group such as a political community. One meaning of "politic" is "prudent," and one may determine the "politic" or "prudent" course

of action, especially in adapting means to ends. How does this form of social prudence relate to "moral"? Although my discussion can only be sketchy at best, I will consider this point in relation to "political" judgments, reasons, and considerations.

V. Politics and Political Considerations

Among the possible positions in opposition to or refusal of service in a particular war, $F_1 - F_4$ could be considered "political" in nature. We might say of F_1 ("the war is not in the national interest") that it is "purely political," claiming that it does not refer to any considerations but political ones. Although ordinary usage would appear to support such a statement, neither the formal nor the social material criteria of morality require that F_1 be classified as "purely political" in the sense of totally "nonmoral." One difficulty, of course, is transposing criteria that might be clear for "moral" judgments and considerations about individual conduct in interpersonal settings to the political order. Nevertheless, policy-makers and citizens could construe the national interest as a "moral" consideration (or at least a "semimoral" one) since it can be universalized (on some interpretations), prescriptive, and may be overriding. Furthermore, national interest may not violate the standard of otherregardingness, for it invokes the interests of some persons other than the agent. The same point could perhaps be made about group interests (e.g. labor unions) in pluralistic politics. But such interpretations are somewhat strained.

One possible argument for classifying F_1 's judgment (and F_3 's too) as political is that (1) it is based on the sorts of considerations that policy-makers examine and the type of reasoning they employ, and (2) it is the sort of matter that can and should be resolved through the political process.

Let me start with the second reason, which requires several comments. First, as Giovanni Sartori contends, "in order to find our way in the differentiations among politics, ethics, law, economics and so forth, it is necessary to refer to

the structural differentiation of human aggregations. Perhaps because of a lack of categories, perhaps for other reasons, the fact is that only the field of ethics, which is the most ancient and the most developed, escapes reference to a structural underpinning.³⁵ In contrast to "ethical," the other terms such as "political and "legal" signify a locus, a site of behavior, a system, which is "a constellation of structures, roles, and institutions." Thus, it is necessary to refer to that system in discussing "political" judgments, in distinction from "ethical" ones, but this necessity poses a special danger: it is difficult to state the criteria of "political" without implying a specific type of political system such as a liberal constitutional democracy. If "political" is understood as referring to a system within the social structure, $F_1 - F_4$ but also most of the other positions could be understood as "political" in that they fall within the political sphere, are directed toward particular policies and laws which they want to change, etc. But this sense of "political" would not deprive any of these positions of the label "moral" or necessitate their classification as "nonmoral." Indeed, they could be both moral and political.

Second, we establish procedures and processes for reaching certain decisions. Admitting that "in a sense all decisions are moral decisions," Virginia Held goes on to emphasize that "we seem to make moral decisions to treat given ranges of decisions some other way, to adopt more limited decision procedures for such ranges."³⁶ We assign a number of matters to the political process, to be determined through established procedures (such as voting, etc.), and, within limits, abide by the outcome without reexamining the procedures and process each time. On these grounds F_1 might properly be viewed as political. Such a judgment can only be made within a particular political system (or within a proposal about a political system). Sometimes, however, we may feel that constitutional or moral limits (cf. G_4 and B as well as a version of C that insists that the war is being conducted unjustly) have been violated, and in some cases agents may make moral and political

("moral-political"?) decisions to oppose those outcomes and perhaps even to work for a new system. (The dispute about which political procedures are desirable is itself a political dispute.)

Certain types of considerations seem to belong to political procedures and processes and claim the attention of political agents, who usually reason in certain ways. If there were no disagreements about ends, goals, and purposes in human life, there would be no politics. Among angels and beasts there is no politics--among angels, presumably, there is complete concord of purpose; among beasts there is no capacity for projecting ends. The context of politics and political thought is the collision of some human ends and purposes. Where such a collision is absent, the only remaining questions are technical: how do we achieve our goals? But such questions are for the experts. The political question par excellence is "what ought we (not I) to do"?

Variouly viewed as a problem of order and freedom, unity and diversity, public and private, political life is a matter of "continually creating unity, a public, in the context of diversity, rival claims, unequal power, and conflicting interests." Although the enterprise of politics is conducted within certain procedures and by certain processes, it is aimed at "the conciliation of differing interests."³⁷ Its primary mode of reasoning and justification is teleological (right and wrong depend on the ends and consequences of actions and policies). Its reasons rest on ends and consequences. But only a doctrinaire view of politics would insist that deontological considerations (that some things are right or wrong independent of their ends and consequences) are totally excluded. Deontological considerations (whether moral, legal, or constitutional) may well set limits on the ways certain ends are pursued; among the principles of a political order may be certain convictions that set limits on what the community can do in achieving other goals. For instance, the right of free speech is not to be abridged. Such deontological considerations may be prima facie rather than absolute requirements.

Even if teleological reasoning is primary in political discourse and argument, it is not a necessary or a sufficient condition of "political." For moral reasoning apart from politics may well be teleological, and political reasoning may well include deontological considerations.

F₃ which argues that the war is wrong because it can't be carried through to victory appears to be making a judgment of political prudence. His pragmatic calculations are of the sort that we may (morally) decide should be resolved through the political process since people of good will may have different assessments of probable success. Perhaps F₃ is reducible to F₁ on the grounds that it is not in the national interest to risk political survival, independence, etc. for a losing cause. It may be close to F₂ in that it is a judgment of proportionality although its cost-benefit analysis is limited to one's own nation. In either case, its classification would probably follow the pattern of F₁.

F₂ which insists that the war is wrong because the evil results will outweigh the good ones is an example of consequentialist reasoning. What are the grounds for calling it "political" (in the sense of "nonmoral")? In contrast to F₁ which argues only from the standpoint of the national interest, F₂ is a prescriptive, overriding, and universalizable judgment about the effects of policies on others and thus satisfies both the formal and social material conditions of morality. If we classify F₂ as "political" (as often happened during the Vietnam War), we seem to be implying the following points. Given our commitments to democratic procedures, the question about the proportionality of good and evil results of policies is properly political, in the sense that we have (morally) established certain procedures and processes for arriving at such decisions. Furthermore, that question can only be answered by a mode of calculation that is properly political. If, however, F₂ argued not a point about proportionality but rather a point about the war's conduct (for instance, as a violation of the principle of discrimination between combatants and noncombatants based either on morality or International law), his

position would be deontological and more properly moral. Such uses of the label "political" for judgments and considerations obviously presuppose commitments to resolving certain conflicts within political procedures or to viewing certain types of considerations as properly political. Our discussion of the criteria of "moral" in contrast to "nonmoral" does not provide any grounds for a neutral, logical distinction between "moral" and "political" that would permit us to classify F_2 as purely political.

When we say that the President vetoed a bill "for purely political reasons" or "only for political reasons," we may imply that he actually thought the bill was in the public interest and that he would have signed it if he had not been swayed by his interest in retaining power to yield to public opinion or some group, or by his interest in influencing Congress to act in a certain way later. Or we might agree with the President's decision and yet criticize his reasons as "purely" or "only" political. In such usage, we strip the term "political" of any positive moral connotations. "One says 'only' [as in "he did it only for political motives"] because something is done for the wrong or for not quite the right reason--done for one reason where there is another and nearer reason for doing it anyway." ³⁸

The meaning of "political", as Alan Gewirth has suggested, ³⁹ fluctuates between moral (e.g. Aristotle, Rousseau, and Hegel) and amoral (e.g. Machiavelli) poles, just as the term law does. The moral pole often "subsumes ethics under politics on the ground that while every community aims at some good, (as Aristotle insisted) 'the state, the political community, aims at the supreme good'." The amoral pole understands politics as the use of deception, force, coercion, and even violence to achieve the end of power as rule and domination. Other definitions of "political" falls between these poles. One is the rhetorical--"political" indicates the use of persuasion, influence, pressure, etc. to obtain some end; here the emphasis falls on influencing others' acts and attitudes. Another is the administrative--"political" indicates the application of rules to the affairs of some community. The phrase "academic politics" may suggest the administrative,

while the description of a department chairman as a "political operator" may suggest the rhetorical.

In the contemporary context, a number of political theorists accentuate the moral qualities of politics and define it in those terms, while many political scientists who are more empirically oriented define politics in terms of amoral and rhetorical themes, stressing interest, power, and influence. Neither side can claim a decisive victory by appealing to ordinary usage. Within the family of words relating to politics and deriving from the same root, we can discern different emphases. The adjective "politic" which comes very close to "prudent" and "expedient" and the noun "politics" best fit the amoral concept with its emphasis on interest and power. Both the adjective "political" and the noun "policy" are more neutral, although "policy" perhaps suggests more public and moral concerns. Indeed, several political theorists such as Wolin and Arendt use "political" as a substantive--"the political"--and eschew "politics" except to describe current realities. ⁴⁰ The proponents of a moral definition of politics may intend to offer not a reportive but a reformative definition, for which ordinary usage is instructive but not critical. They may justify their definition on the grounds that it enables us to understand and direct our activities better than alternative definitions.

Surely the most difficult issues in the relations of ethical and political judgments derive from certain conceptions of normative ethics (e.g. the law of love) as applied to normative understandings of politics (e.g. the realist view of politics as dominated by self-interest and the libido dominandi). As Max Weber's classic essay "Politics as a Vocation" stressed, there are two very different moral perspectives on political life: Gesinnungsethik and Verantwortungsethik. The former, variously translated as ethics of ultimate ends, absolute values, and intentions, is clearly deontological; it may even hold, fiat justitia, ruat caelum, and it is obviously inimical to the prudential calculation of consequences. The ethics of responsibility, by contrast, takes account of average

human deficiencies, calculates the costs, and is willing to use "morally dubious means or at least dangerous ones" (especially coercive and violent ones) for worthy ends. Yet these "ideal types" for Weber are "not absolute contrasts but rather supplements."⁴¹ To insist that one perspective of the other be defined as exclusively "moral" or "political" is to overlook the point that they are both possible perspectives on the relations of morality and politics.

Although political reasoning and argument are largely (but not necessarily and exclusively) teleological and consequentialist, many judgments in the political arena may be classified as moral as well as political.⁴² One difficulty has to do with group interest and national interest; if they are classified as egoism writ large, they may be considered nonmoral (at least on most interpretations of otherregardingness and universalizability). If, on the other hand, they are not basically egoistic or if they meet the conditions of universalizability and otherregardingness, political prudence may qualify as a form of moral judgment. Although the policy-making process is complicated by the number of parties affected by decisions, the range and magnitude of effects, etc., the reasons for policies may be appropriately considered as moral, not merely nonmoral or political, if the formal and material criteria of "moral" are met. While the sorts of considerations and the mode of reasoning are not sufficient to distinguish political judgments and arguments from moral ones, we do assign certain matters to decision-making procedures and processes that are "political" in that they are concerned with the conciliation of differing interests. But the logic of the terms "political" and "moral" does not dictate that such matters (and decisions about them) are merely or purely political.

VI. Religion and Theology

Our war resister # 11 insists that "Only one war can be just--the battle of Armageddon which God will command and direct." Since the current war does not meet these religious criteria, it must be condemned as unjust. 11's judgment appears to be based on nonmoral, specifically religious, reasons rather than moral ones. But what is to be gained by this sort of classification? What are the issues in the distinction and relations between religion and morality or theology and ethics?
43

Definitions of religion are almost as controversial as definitions of morality. Some interpreters suggest that we start looking at religion in distinction from morality by asking about their respective functions: while morality's function is to facilitate human cooperation, religion's function is to deal with problems of meaning (such as suffering and death) on cognitive, emotional, and practical levels. Although functional analysis is suggestive, it does not take us very far, and the major dispute about the definition of religion parallels the debate about the formal and material conditions of "morality." Must "religion" satisfy formal criteria such as "ultimacy" or "primacy," or must it have a certain content such as "sacredness" or "transcendence"? Furthermore, can either set of criteria (or even both sets together) be viewed as necessary and/or sufficient conditions of "religion"?

Let's look briefly at some examples (and difficulties) of these different sorts of definitions. Paul Tillich defined religion in terms of "ultimacy" or "ultimate concern": "Religion is the state of being grasped by an ultimate concern, a concern which qualifies all other concerns as preliminary and which itself contains the answer to the question of the meaning of our life."⁴⁴ The condition of "ultimacy" (whether applied to concern or to objects of concern) seems to be neither necessary nor sufficient, for some religious objects such as "spirits" may not be "ultimate" to their believers and some principles (such

as the principle of utility) that we would count as non-religious could satisfy this criterion. Perhaps a religious action-guide claims priority or supreme authoritativeness, but this condition, as we have seen, is also proposed as one formal condition for moral action-guides as well (although it is the one that I declined to emphasize on the grounds that it begged too many questions at least in its strong form). Any action-guide that is taken with sufficient seriousness would seem to qualify as "religious" by this definition.

Without offering complete arguments for a definition in terms of some beliefs or the status of some objects, I think that a definition of "religious" in terms of sacredness is more promising. It avoids some terms such as supernatural that presuppose a specific religious worldview (with a distinction between nature and supernature) and thus are ethnocentric. Yet it seems broad enough. David Little and Sumner Twiss define a "religious statement" as "a statement expressing acceptance of a set of beliefs, attitudes, and practices based on a concept of sacred authority that functions to resolve the 'ontological' problems of interpretability." 45

Religion, as defined, may affect the moral life in numerous ways. Some of those who emphasize this point insist that it is also necessary to challenge the formal criterion of universalizability in order to acknowledge this influence or, more specifically, in order to do justice to "Christian ethics," "Jewish ethics," etc. But the fact that religions may offer motivations for being moral and may affect character, decisions, etc. is no reason for eliminating the requirement of universalizability. We are interested in the process of reason-giving, in the justification of decisions and particularly policy-recommendations. As Frankena insists, one may correctly maintain that "many aspects in the shaping of a life, moral or religious, need not be subject to the universalizability requirement. Only normative and evaluative judgments are."⁴⁶ Here the issue is not between "religious" and "moral" but rather between judgments and other aspects of the

moral life which need not be subject to the universalizability requirement in order to be moral. Even if they meet the condition of universalizability, religious systems may well be normative or value systems without thereby being moral ones.

If one takes the purely formal criteria, religious action-guides that are universalizable, prescriptive, and overriding could qualify as moral. Excluding the criterion of universalizability (or at least some of its versions), James Gustafson holds that since religious action-guides are prescriptive and overriding, they should be counted as moral or not merely as nonmoral (i.e. religious). They are both religious and moral.⁴⁷ Thus, there can be a religious qualification of morality or a theological qualification of ethics. It is also possible to interpret the criterion of universalizability so that religious action-guides also qualify as moral ones.

One objection to taking formal features of morality as sufficient rather than merely necessary is that they undercut or make it difficult to explicate our ordinary distinctions between morality and law, religion, etc. But, given the view that moral judgments must meet a social material condition, can religious action-guides meet this condition? When H bases his argument on God's will, isn't he thereby excluding all reference to human welfare or harm? Denying that the condition of concern for human welfare or harm writes "humanism" or "secularism" into the definition of morality, G. J. Warnock adds,

I suspect that religious views differ from 'humapist' views, not by denying the essential moral relevance of human benefit or harm, but rather by incorporating very different beliefs as to what really is good or bad for human beings. The religious believer finds in a supernatural order a whole extra dimension of pre-eminently important gains and losses, benefits and harms; his difference with the non-believer is not on the question whether these are of moral significance, but simply on the question whether they are real or chimerical. He might also wish to expand what might be called the moral population to include moral beings supposed not to be human....⁴⁸

Or "moralities with a transcendental dimension have a greater logical freedom with respect to their content than moralities which have no such dimension...."⁴⁹

To take an extreme statement, one might hold on some religious views that it is right to destroy another's body in order to save his soul. If such a statement meets the formal conditions of morality, it may also meet the social material condition. Religious viewpoints then may qualify morality by offering a different set of facts or a different interpretation of the same facts regarding human welfare. This contention would also hold for other worldviews or large pictures of life, for instance, Marxism, which single out one benefit or harm (such as economic deprivation) or could give preference to some beings (such as future generations) over others. In such interpretations, metaphysical or theological convictions provide insights into humanity and its place in the universe without, however, generating any new basic moral principles, which may be sufficiently clear by ordinary experience or reason. Nevertheless, these "evaluative descriptions" of facts enable us to infer "new derivative duties from basic ones already known to us."⁵⁰ For instance, we may acknowledge a duty of beneficence or, at least, nonmaleficence, but our conception of specific duties will depend on our interpretation of human welfare and harm.

Some religious views on abortion do not hinge on the revelation of a novel basic moral principle but rather on what constitutes human welfare, the weight given to some harms in relation to others, and, especially, when human life begins. A basic moral principle is that we are not permitted to kill other human beings except under well-defined conditions; this principle is shared by most moralities, religious or secular. If one adds an "evaluative description" of the fetus as human being from the moment of conception, the prohibition of abortion follows. This expansion of the population about whom one must be concerned can be construed as religious insofar as one of its premises is held on the grounds of religious authority or on grounds about the beginning of human life that are not merely empirical (but then no statement that human life begins at this or that point in time can be merely empirical). Some recent moral attacks on the prohibition of abortions have accepted this religious version of the beginning of human life for

sake of argument and have then tried to show that the relevant basic moral principle is not non-maleficence but rather beneficence. The question then becomes "how much ought we to do to sustain human life?" rather than "when may we kill human beings?" But even here a religious position might affirm an interpretation of beneficence along the lines of self-sacrifice, going the second mile, etc.

Another interpretation of the relation of religion and morality would take a more stringent view of the criterion of otherregardingness insisting that since human welfare and harm have relatively determinate meanings a religious action-guide must address those meanings if it is also to be moral. From this standpoint, the concept of human welfare has a relatively fixed core "which includes such 'objective' conditions as physical survival, bodily and psychic health, security from arbitrary violence, and the like."⁵¹ Little and Twiss contend that when a religious action-guide calls for a violation of this core of human welfare, perhaps on the grounds that the other's welfare is "really" or "truly" different from these objective conditions, it cannot be considered "moral."

But consider variations of the Abraham and Isaac story. Abraham's conviction that he should sacrifice his son, even if he conceived this to be truly in his son's best interests, would not be "moral" but only "religious" given the Little-Twiss condition. But what if Abraham decided to sacrifice his son because God had promised to make the people "happy" if he performed this act? Little and Twiss presumably would deny that this is a moral argument since survival is part of the core concept of human welfare whereas happiness is not. But suppose that Abraham felt that God had commanded this sacrifice as expiation for his people's sins and that he should perform it in order to stop God from slaughtering several thousand people. Here Abraham does not disregard Isaac's physical welfare for the sake of Isaac's "real" welfare; nor does he sacrifice Isaac's physical welfare for the sake of others' happiness. Rather, Abraham balances Isaac's death against the

deaths of several thousand persons. Is this to be a "moral" decision or a "religious" one? Does the presence of a "transempirical" premise (that God will do what he said he will do) render this a "religious" argument? Would it be a mixed "religious" and "moral" position?

One possibility is that we set certain standards of evidence regarding causal processes, etc., and do not consider positions that fall short of these standards as moral (at least in a critical sense although they may be moral in an anthropological sense). For, as Ronald Dworkin contends,

If I base my position on a proposition of fact ('homosexual acts are physically debilitating') which is not only false, but is so implausible that it challenges the minimal standards of evidence and argument I generally accept and impose upon others, then you would regard my belief, even though sincere, as a form of rationalization, and disqualify my reason on that ground.⁵²

Perhaps some religious beliefs, especially if they contradict basic assumptions about human welfare, may be disqualified in the same way. But if we work from this perspective, we are clearly offering more than a neutral classification of reasons and statements. Indeed, the attempt to draw some sharp distinctions between "religious" and "moral" reasons may presuppose a value-judgment to the effect that religious reasons for policies must be viewed with suspicion and perhaps even disqualified at least in a society marked by a sharp separation of church and state and religious pluralism. Here, again, what is actually an issue of how much power and influence certain sorts of beliefs should have in a society is transmuted into a putatively neutral, logical analysis of terms.

VII Conclusion

Because of space requirements, I am unable to include a projected section on legal action-guides and considerations, which would have considered issues raised by F_4 and G and examined the logical and conceptual relations between law and morality. It would have treated two major approaches in jurisprudence as analogous to the two major options in defining morality: formal conditions and material conditions. Those who insist on a moral content in the definition of law (e.g. "an unjust law is no law at all") stand in opposition to those who define law in more formal terms of commands, rules, etc. although there are several mediating interpretations between "natural law" and "positivism" (two widely used but unhelpful labels).

I have tried to highlight several issues in the identification of "ethical" or "moral" judgments, reasons, and action-guides, concentrating on three formal conditions and one social material condition, and I have dealt with the distinction between "moral" and "nonmoral" in relation to ideals, prudence, and political and religious considerations. Although I have been mainly concerned with analysis, I think that a good case can be made that the conditions of prescriptivity, universalizability, and otherregardingness are necessary and sufficient conditions of moral judgments and action-guides, but I concentrated on the implications of taking either a formal or a material definition for such topics as ideals and prudence. I did, however, explicitly exclude finality or overridingness, at least in its strong or absolute sense, from the criteria of "moral", mainly because it begs too many questions, particularly about whether one should be moral and what weight moral reasons should have in public debate. Attempts to classify reasons as "moral" and "nonmoral" are not too misleading and dangerous if the classifiers do not assume that "moral" reasons are ultimately authoritative or are the final arbiters. Moral reasons may well have this place but definitions should not foreclose such important human and public questions. Thus, even if basically prudential or egoistic reasons

are nonmoral, their function is akin to moral action-guides, and the distinction between moral and nonmoral should not prejudge their weight.

In some social and political conflicts one party may have the power to punish or restrain the other. Consider the case of government X and resister A, whose position that the war is wrong satisfies only the formal criteria of morality (i.e. avoids consideration of effects on others). Frankena insists that the formal definition of morality "makes it unclear just what moral justification society could have for punishing or restraining any individual who is acting 'conscientiously' in accordance with his own AC [action-guide], whatever this may be and whatever his action is." ⁵³ We have already seen that this dispute could be called moral without attributing moral claims to both sides, but, given only formal criteria, both sides are playing the moral game. The moral justification for the government's restraint and for A's resistance (flight, etc.) would come from substantive moral positions. We are only concerned with whether the reasons can be construed as moral not whether they can be actually justified on substantive grounds. Furthermore, it is not at all clear that insisting on a social material condition of morality in any way avoids this issue. For a dispute between government X and resister B or C, both of whom consider effects on others, is still a dispute within morality, between two substantive moral positions. X may restrain or punish B or C if they disobey or flee on the grounds that their acts are "morally unjustified" although their reasons are recognized as moral ones (as opposed to non-moral). A definition of "moral" over against "nonmoral" cannot resolve such disputes or even make them easier to resolve. Frankena's objection appears to trade on the ambiguity of "moral," at this point taking it as opposed to "immoral" instead of "nonmoral." Indeed, his objection hallows the liberal notion that there can be no moral justification for the state's interference in conduct unless there is harm or the imminent danger of harm to others or to society. This position may well be true (and I am inclined to think that it is, with some qualifications), but it

should not be declared true by the definition of "moral." It is a matter for substantive debate.

One major concern about all the definitions we have examined is that certain sorts of reasons may receive a great deal of power and influence by virtue of their classification as "moral" over against "nonmoral." An allegedly neutral, logical analysis may serve as a substitute for substantive debate, not only setting the terms of the debate but also determining the weight of sorts of reasons.

"When I use a word," Humpty Dumpty said, in rather a scornful tone, "it means just what I choose it to mean--neither more nor less."

"The question is," said Alice, "whether you can make words mean so many different things."

"The question is," said Humpty Dumpty, "which is to be master--that's all."

Notes

1. In this paper I use a variety of expressions such as considerations, reasons, and action-guides as shorthand for a range of nouns such as arguments, rules, principles, etc. that might be modified by "ethical" or "moral."
2. See Parsons, "Christianity and Modern Industrial Society," in Sociological Theory and Modern Society (New York: The Free Press, 1967); most of the essay is reprinted in James F. Childress and David B. Harned, eds. Secularization and the Protestant Prospect (Philadelphia: The Westminster Press, 1970), pp. 43-70.
3. Thomas Luckmann, The Invisible Religion (New York: The Macmillan Co., 1967), p. 101.
4. I shall use the terms "moral" and "ethical" interchangeably in this discussion although one might wish to distinguish them in some contexts. Cicero apparently formed the Latin word moralis (from mores) to translate the Greek term ethikos. Etymologically their meanings are very similar, stressing manners, character, and customs. Contemporary usage suggests some rough but not very precise distinctions between them. "Ethics" often expresses more intellectual perspectives or even theories, while "morality" often refers more directly to practice and actual conduct. Recent philosophical discussion has been focused on the concept of "morality" (not "ethics"). Likewise, moral (rarely "ethical") principles and arguments have been the subject of discussion.
5. William K. Frankena, "The Concept of Morality," in The Definition of Morality, edited by A.D.M. Walker and G. Wallace (London: Methuen, 1970), p. 149. Frankena uses the terms "descriptive-elucidatory" and "normative," the latter of which I avoid because of its use also in normative ethics, although I recognize that not all normative judgments are moral ones. Frankena's approach is clearly one of normative metaethics, and he at times appears to offer normative moral reasons for his distinction between moral and nonmoral.
6. See R. M. Hare, Freedom and Reason (London: Oxford University Press, 1963), pp. 146 ff. Contrast William K. Frankena, "The Concept of Morality," The Definition of Morality, pp. 160-161. See my discussion in Part III below. Much of my discussion in this paper has been influenced by a number of Frankena's essays.
7. Joel Feinberg, Doing and Deserving: Essays in the Theory of Responsibility (Princeton, N.J.: Princeton University Press, 1970), p. 18, fn. 10.
8. W.D. Hudson, Modern Moral Philosophy (Garden City, N.Y.: Doubleday, Anchor Books, 1970), p.2.
9. These four criteria which appear in various forms in the literature have been thoroughly discussed by William Frankena in several places (for instance, "The Concept of Morality" in The Definition of Morality). Other philosophers have identified other criteria although I am inclined to think that they are subordinate to these four. Thus G. Wallace and A.D.M. Walker consider definitions in terms of particular forms of sanctions that are associated with moral rules and principles, and in terms of the importance of moral rules and principles. It is not at all clear that importance can be distinguished from overridingness, unless one is thinking about importance for society. Not is it clear that a discussion of sanctions, either internal or external, would be useful, for sanctions derive from morality's authoritativeness. See Wallace and Walker, eds., The Definition of Morality, "Introduction."

Also in that volume, see T.L.S. Sprigge, "Definition of a Moral Judgment," which emphasizes sanctions, and Neil Cooper, "Morality and Importance."

10. R. M. Hare in Freedom and Reason appears to defend all three formal criteria, especially the first two, while explicitly rejecting the material one. By taking "prescriptivity" in a limited and weak sense, I am not doing justice to Hare's position, although this is sufficient for our purposes.

11. Hare, Freedom and Reason, pp. 139-40.

12. Ibid., pp. 168-69.

13. Ibid., p. 195.

14. See William K. Frankena, "The Concept of Morality," The Journal of Philosophy, LXXIII (1966), reprinted in Kenneth Pahl and Marvin Schiller, eds., Readings in Contemporary Ethical Theory (Englewood Cliffs, N.J.: Prentice-Hall, 1970), p. 394. Cf. also the longer earlier version of this paper with the same title, "The Concept of Morality," The Definition of Morality.

15. See Alasdair MacIntyre, "What Morality Is Not," Philosophy (1957):325-35. Reprinted in The Definition of Morality, pp. 26-39.

16. See William K. Frankena, "The Concept of Morality," The Definition of Morality, p. 154.

17. G. J. Warnock, Contemporary Moral Philosophy (New York: St. Martin's Press, 1967), p.54. Several of Frankena's essays discuss and propose the social material criterion. Other philosophers who have proposed versions of this criterion include Kurt Baier, Bernard Williams, J. Kemp, David Gauthier, Stephen Toulmin, and Philippa Foot. Among the proponents of some version of formal conditions of morality are R. M. Hare, H.L.A. Hart, W. D. Falk, and John Ladd.

18. Warnock, Contemporary Moral Philosophy, p. 69, cf. pp. 60-61. Although these are matters of judgment, they are not matters of moral judgment, and Warnock insists that the charge of circularity does not apply when one then defines morality in terms of these "facts." In this paper I cannot, of course, deal with the debate about whether this approach can avoid or rebut the charges leveled against "naturalism," which is at the heart of the debate.

19. See David Little and Sumner B. Twiss, "Basic Terms in the Study of Religious Ethics," Religion and Morality, edited by Gene Outka and John P. Reeder, Jr. (Garden City, N.Y.: Anchor Press/Doubleday, Anchor Books, 1973), pp. 54 ff.

20. "The Concept of Morality," The Definition of Morality, p. 156. Emphasis added.

21. Ibid., p. 157.

22. See Hare's charge in Freedom and Reason, p. 163. Contrast Frankena, "The Concept of Morality," Readings in Contemporary Ethical Theory, pp. 396, 394. It is interesting that in normative ethics, a number of different parties to the dispute are utilitarians or mixed theorists. But these normative ethical positions bear no close relation to their views of the nature of morality. Regarding distributive justice, Hare writes, "I do not think that the difference between naturalism [which, in this context, would include the social material definitions

of morality] and prescriptivism [his own position] has any bearing on the matter--which is hardly surprising if, as I think, there is no substantial difference between the parties on any matter which is going to affect our actual moral arguments." "Wrongness and Harm," Essays on the Moral Concepts (Berkeley and Los Angeles: University of California Press, 1972), p. 96.

23. Another possibility is to distinguish between "strong" and "weak" senses of overridingness or priority. Strong priority means moral action-guides always take precedence over conflicting nonmoral action-guides; weak priority indicates a prima facie priority so that moral action-guides cannot always be ignored or overridden without ceasing to be moral. Little and Twiss develop this interpretation and defense of weak priority in "Basic Terms in the Study of Religious Ethics," Religion and Morality, p. 48. I would also emphasize that weak prima facie priority means that moral action-guides must always be taken seriously; they cannot be disregarded although they may be overridden. Furthermore, one might extend the analysis to indicate presumptions, burdens of proof, etc. Although one might distinguish finality or ultimacy and priority, I am conflating them in my discussion.

24. See Strawson, "Social Morality and Individual Ideal," in Readings in Contemporary Ethical Theory, edited by Kenneth Pahel and Marvin Schiller, pp. 344-59. Although space limits prevent me from pursuing the point in this paper, frequently one does not try to persuade the others that they ought to adopt one's ideals, which are purely personal or rest on religious and other beliefs. In the debate between government X and resister E, the latter would probably ask for a personal exemption rather than trying to persuade X that conscription itself is wrong.

25. See Hare, Freedom and Reason, pp. 146ff.; W. D. Falk, "Morality, Self, and Others," in Morality and the Language of Conduct, edited by Hector-Neri Casteneda and George Nakhnikian (Detroit: Wayne State University Press, 1963), pp. 25-67; Frankena, "The Concept of Morality," The Definition of Morality, pp. 159-163.

26. This option, which I find unsatisfactory, is similar to Frankena's strategy in his discussion of Hare's example of a debate about ideals in relation to a "stripper" in a club catering to middle-aged businessmen. "The Concept of Morality," The Definition of Morality, p. 160; cf. Hare, Freedom and Reason, pp. 147f.

27. Warnock, Contemporary Moral Philosophy, p. 59.

28. Cf. W. D. Falk in "Morality, Self, and Others," in Morality and the Language of Conduct.

29. Contrast Hare who thinks that such an action-guide may be prescriptive (and perhaps taken as overriding) without being universalizable. He distinguishes "ought₁" (which meets both formal and social material conditions), "ought₂" (which is prescriptive and universalizable), and "ought₃" (which is prescriptive but not universalizable). Although Hare does not think we actually ever use "ought" in the third sense, he considers it: "'Ought₃' has to do with questions of self-interest which is not universalized-self-interest, and the interest of groups, such as my family, and my country, which are defined by reference to an individual." Freedom and Reason, p. 165.

30. See "The Concept of Morality," The Definition of Morality, p. 156.

31. Warnock, Contemporary Moral Philosophy, p. 49, which summarizes the position taken by Baier and Gauthier, among others, as well as his own.

32. Josef Pieper, Prudence. Translated from the German by Richard and Clara Winston (New York: Pantheon Books, 1959), pp. 21-22, 53.

33. Cf. W. D. Falk's perceptive comment: "This was, in effect, the view of the old Natural Law moralists--Hooker, Grotius, Puffendorf: the social virtues derive joint support from our natural concern for our own good and for that of society. Hobbes streamlined this account by denying the second, which provoked subsequent moralists to deny the first. Both Hobbes's sophisticated toughness and the well-bred innocence of the academic moralists since are distorted visions which are less convincing than the unsqueamish common sense of the philosophers and divines of earlier times." "Morality, Self, and Others," in Morality and the Language of Conduct.

34. This paragraph derives from Falk's account, see ibid.

35. Giovanni Sartori, "What is 'Politics'?" Political Theory 1, no. 1 (February 1973): 17-18. Contrast J. R. Lucas who uses the term "political" in its undifferentiated, wide, original sense "in which it applies not only to politics in the modern, narrow, sense, but to social and legal affairs, and all that pertains to men's public life." The Principles of Politics (London: Oxford University Press, 1966), p. 20, fn. 1.

36. Virginia Held, "Justification: Legal and Political," Ethics 86 (October 1975).

37. Hanna Pitkin, Wittgenstein and Justice (Berkeley and Los Angeles: University of California Press, 1972), p. 215; Bernard Crick, In Defense of Politics (Baltimore: Penguin Books; Revised Pelican Edition, 1968), p. 148.

38. W. D. Falk, "Morality, Self, and Others," Morality and the Language of Conduct, p. 39.

39. Gewirth, "Political Justice," Social Justice, edited by Richard Brandt (Englewood Cliffs, N.J.: Prentice-Hall, 1962), pp. 119-20.

40. This discussion of ordinary usage stems largely from Hanna Pitkin, Wittgenstein and Justice, pp. 214-15.

41. Weber, "Politics as a Vocation," in From Max Weber: Essays in Sociology, ed. and trans. Hans Gerth and C. Wright Mills (New York: Oxford University Press, 1946), pp. 118ff.

42. Virginia Held seems to claim too much about the teleological character of political reasoning and the deontological character of legal reasoning although some of her points certainly hold. "Justification: Legal and Political," Ethics 86 (October 1975): 1-16.

43. Both religion and morality, which are usually paired, relate more clearly to practice, while both theology and ethics imply more reflection upon practice, James Gustafson writes, "Theology is reflection on human experience with reference to a particular dimension of the human experience denoted 'religious.'" The Contributions of Theology to Medical Ethics. The 1975 Pere Marquette Theology Lecture (Theology Dept., Marquette University, April 1975), p. 4, cf. p. 6-7. In these remarks I shall concentrate on definitions of "religion," assuming that

theology is reflection on "religious" objects, experiences, etc.

44. Tillich, Christianity and the Encounter of the World Religions (New York: Columbia University Press, 1963), p. 4; cf. Dynamics of Faith (New York: Harper and Row, 1958), pp. 1-12. See the good critique of Tillich's definition in Rem B. Edwards, Reason and Religion (New York: Harcourt, Brace, Jovanovich, 1972), pp. X 3-13.

45. Little and Twiss, "Basic Terms in the Study of Religious Ethics," Religion and Morality, p. 62.

46. Frankena, "Conversations with Carney and Hauerwas," The Journal of Religious Ethics, III (Spring 1975): 56. Both Fred Carney and James Gustafson call into question the universalizability requirement for "moral" in order to make room for "religious ethics." See Carney, "On Frankena and Religious Ethics," The Journal of Religious Ethics, III (Spring 1975): 7-25 and James M. Gustafson, Can Ethics Be Christian? (Chicago: University of Chicago Press, 1975), passim. I think that Frankena's point holds against both positions as far as judgments are concerned.

47. Gustafson, Can Ethics Be Christian?, p. 177: "On the basis of the assumption that certain values and principles have an obligatory character within a 'way of life' and that the Christian history and community call for a way of life grounded in the Christian story, it is fitting to call these Christian ethical principles and values." My emphasis. Cf. p. 167: "It is a moral principle in the sense that it determines the 'conscience' of the believer...." But Gustafson also writes (p. 117), "It [a principle of nonviolence] is a moral principle because actions governed by it have moral, or at least human value consequences for others." It is not clear whether he considers this social material concern or effect to be a necessary or sufficient condition.

48. Warnock, Contemporary Moral Philosophy, p. 79, fn. 27.

49. Bernard Williams, Morality: An Introduction to Ethics (New York: Harper and Row, Harper Torchbooks, 1972), p. 84.

50. William K. Frankena, "Is Morality Logically Dependent on Religion?" Religion and Morality, edited by Gene Outka and John P. Reeder. I cannot deal with a number of the important issues surrounding the "is -ought" debate.

51. David Little and Sumner B. Twiss, Jr., "Basic Terms in the Study of Religious Ethics," Religion and Morality, p. 74.

52. Ronald Dworkin, "Lord Devlin and the Enforcement of Morals," Morality and the Law, edited by Richard A. Wasserstrom (Belmont, Cal.: Wadsworth Publishing Co., 1971), pp. 63-64.

53. "The Concept of Morality," The Definition of Morality, p. 159. My emphasis.

BASIC ETHICAL PRINCIPLES IN THE CONDUCT OF BIOMEDICAL AND
BEHAVIORAL RESEARCH INVOLVING HUMAN SUBJECTS

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I. INTRODUCTION

Philosophy serves us best by helping us be clearer about the meaning of activities such as knowing and valuing. Philosophy does not simply map actual human activities in conceptual terms. Rather, it provides a portrayal of the conceptual topography of the possible. Thus, when individuals inquire after the basic ethical principles which should underlie the conduct of biomedical and behavioral research, they are not (or should not) be asking what principles actually do underlie such research, or even what principles we would be most comfortable with. After all, our conduct may be influenced by a complex of prejudices which would incline us to do things which we would, after more penetrating reflection refrain from doing. This is not to say that ethics deduces guidelines for human conduct from some divine perspective. Surely not. Ethics, as a philosophical enterprise, is best conceived as an attempt to negotiate diverse moral intuitions. Ethics is the logic of a pluralism in the sense that ethics is an attempt to find the most general grounds or bases for judging the rightness and wrongness of conduct. Unlike religious ethics, or particular legal traditions, philosophical ethics hopes for general principles of conduct discoverable by disinterested reflection, apart from either grace or cultural prejudice. Though such a disinterested perspective cannot be attained, one can move towards such a vantage point by attempting to lay out ever more clearly general principles of moral conduct. It can thus function as a regulative ideal in the attainment of greater objectivity in moral judgments, in the sense of striving for greater intersubjectivity (i.e., principles more likely to enjoy general assent).

What I will provide here is an analysis of what is at stake with regard to moral conduct in the case of biomedical and behavioral research involving human subjects. To begin, I will hold that in general there are two central and different types of concerns at issue in experimentation involving human subjects: (1) questions bearing on respect for persons as moral agents, and (2) questions bearing on the achievement of goods and values which humans in general esteem.¹ The first set of considerations turns on respect for the freedom of individuals. The second set of considerations turns on the best interests of such individuals, and of the human community in general.

Most people will readily agree that there are goods and values which humans esteem. There are, though, some individuals who hold that freedom is a non-scientific chimerical concept.² Since appeals to freedom in concepts of free and informed consent are so important to the ethical issues in experimentation, it is worth indicating here the central role of the concept of freedom for morality. Holding that persons are free is not a metaphysical thesis, but the statement of a proposition that must be presupposed if any talk about human conduct is to make sense.³ If persons are not free to choose good reasons over bad, but are caused to embrace some reasons rather than others, then there is no possibility of anyone being right or wrong about anything--and no need for this essay. For in that case, persons would simply be caused to hold that some activities were more or less successful, correct or incorrect, valid or invalid. To be right or wrong about matters of fact or logic presupposes that one could hold certain propositions to be true or valid on the basis of good reasons, rather than being caused to assert that they are true or valid.

The same holds for moral conduct. One must presuppose that persons can freely choose to do one thing rather than another if one is to mean anything else by morally correct (or incorrect) conduct than that one is reinforced (or negatively reinforced) by such conduct, or the prospect of such conduct, and that one is reinforced by others engaging in (or not engaging in) such conduct. Morality presupposes that individuals are worthy of blame or praise because they can freely choose between different lines of conduct. If that is not the case, then we are simply caused to engage in particular behavior and to call certain behavior moral or immoral, and there is no possibility to mean anything by 'right' or 'wrong' other than that one is caused to call some things right or wrong. In that case, any serious talk of ethical principles must cease. For example, the proposition, "Nazi experiments on non-consenting human subjects were evil," would mean, in the absence of the presupposition of human freedom, only that one was negatively reinforced by the thought of what the investigators did, and was positively reinforced by condemning that conduct. It would not follow that such investigators were actually right or wrong, but simply that one had been caused to feel distressed on account of such conduct. One could choose between those two accounts of human action only if one were able to choose a good account over a bad account--which is to say, if one is free.⁴ It is in this sense that the presumption of freedom is a necessary presumption.

This analysis of basic ethical principles concerning experimentation with human subjects begins then with the presupposition that there is a sense of moral responsibility, and that this sense has meaning only if persons think of each other as being free. Thinking of one another as free is

a logical condition for the existence of a moral community, a community bound together on the basis of mutual respect, rather than force. This is the key consideration in the requirement of free and informed consent--consider, for example, the first requirement of the Nuremberg Code, "The voluntary consent of the human subject is absolutely essential."⁵ Of course, treating persons as members of a moral community (in the case of experimentation, requiring voluntary consent) requires that the members of that community (e.g., the human subjects involved in experimentation) can indeed be treated as free agents--a condition not met, for example, by very young children or many of the very senile, mentally ill, or mentally retarded. In short, not all human subjects can be treated in the same way with regard to ethical considerations in experimentation involving human subjects, because such subjects differ in at least one very relevant consideration, the ability to choose as free agents.⁶

To lay out the basic ethical principles involved in human experimentation will then require: (1) indicating what is due to human subjects used in research out of respect for them as free moral agents; (2) indicating what is due to those human subjects who cannot be treated as free moral agents; and (3) outlining the basic values and goods we wish to support in the practice of human experimentation. In all of this, if one is to speak of basic ethical principles, one must distinguish those principles from procedures or guidelines employed in safeguarding such principles. Thus, requiring free consent is a basic ethical principle, while requiring written consent would merely be a procedural safeguard.

II. A SKETCH OF BASIC PRINCIPLES

The literature concerning human experimentation is rich and varied. It is for the most part concerned with establishing procedures and safeguards in the use of human subjects, rather than providing an analysis of, or clear presentation of, the ethical principles at stake. This lack of clarity stems in part from the fact that any one of the basic procedures involved in ensuring the moral use of human subjects in experimentation involves more than one basic ethical principle. I will hold in the course of this analysis that the literature focuses on three cardinal ethical issues. The first concerns respect for persons as a logical condition for morality. Such respect for persons is not a value among other values.⁷ It is rather the basis for our sense of moral responsibility, and is considered apart from any interest we might have in respecting other persons (e.g., that such respect is useful, or that giving such respect will tend to protect us). It is a concern for rights.⁸ The second and third are concerns for goods and are thus teleological--or goal-oriented.⁹ These ethical principles are:

- A. One should respect human subjects as free agents out of a duty to such subjects to acknowledge their right to respect as free agents.
- B. One should foster the best interests of individual human subjects.
- C. One should have concern to maximize the benefits accruable to society from research involving human subjects, taking into particular regard interest in values such as (1) the

amelioration of the human condition through advances in the biomedical and behavioral sciences and technologies; (2) preservation of human autonomy as a general value;¹⁰ (3) increase in knowledge apart from any consideration of its application to the amelioration of human condition; (4) the personal satisfaction of human subjects derived from their feeling of having contributed to the common good or to the advancement of human knowledge by participation in research.

The first principle is a deontological one in the sense of focusing on a consideration of rights and duties independently of any issue of goods and values. It is an appeal to respect for the freedom of persons whether or not such respect would in the long run contribute to the benefit of society.¹¹ With regard to this principle, experimentation upon unwilling human subjects should be regarded as immoral, even if the results of such experimentation would be of considerable general utility. It would be with regard to such experimentation that the Nazi use of human subjects would be worthy of condemnation, even if it had been the case that such experimentation had revealed extremely useful information not otherwise attainable. Such basic rights cannot be outweighed by goods.¹²

The second principle, concern to foster the best interests of the individuals involved, is a particular type of teleological moral concern, which may or may not be utilitarian in its nature. One may be concerned with the best interests of others (1) out of feelings of sympathy or fellowship, (2)

out of interest in maintaining a society which would act fairly by allowing only that experimentation which redounded to the advantage of the least well-off member of society (and therefore to the best interests of all members on the supposition that a cardinal interest of persons is to avoid the fear of possible exploitation), (3) out of fear that if one did not as a general rule support the best interests of others, one's own best interests would be set in jeopardy, etc. One should notice, though, concern for the best interests of others may not coincide with respecting them as free agents. Free agents presumably can act against their best interests. Therefore, concern for the best interests of others may lead to certain acts of paternalism in which one restricts the freedom of individuals in order to support their best interests. One might think here of rules circumscribing the opportunity of prisoners to volunteer as subjects of human research in that such a liberty is not in their best interests (cf. laws which forbid persons the freedom of selling themselves into slavery).¹³

The third moral principle is as well an axiological or teleological principle. It does not turn on a recognition of a basic duty to perform such actions, but rather on an interest in certain goods or values. This interest can be construed within some formulation of the utilitarian principle of maximizing the greatest good for the greatest number. It is within the context of such considerations that calculations most naturally arise concerning the cost/benefit ratio of particular experiments involving human subjects. The considerations (i.e., goods and values) usually at stake in such calculations include (1) interest in ameliorating the human condition through advance in biomedical and behavioral sciences and technologies, (2) preserving a general

social interest in individual autonomy, (3) supporting the advance of knowledge, and (4) allowing individual humans the satisfaction of contributing to the general good.

It is worth noting that interest in autonomy here is different from the concern to respect persons as moral agents. Here human freedom is considered as one value among others. Thus, it is one thing for an experimenter to gain free consent from a volunteer for participation in an experiment, and another to encourage that subjects consider carefully their consent so as to maximize their opportunity to act freely. In the first principle, respect of freedom functions as a limiting criterion for moral conduct; in this case respect for freedom functions as a value around which to structure a society. It has a utility value. This focus on freedom as a general value for society is a teleological or axiological moral concern. Framed in this context, the "right to autonomy" expresses a general social interest in the value of autonomy. The right to autonomy is thus reducible to talk about interest in values or goods; talking of a "right" here is a sub rosa way of enjoining the pursuit of a value.

The three moral principles of (1) respect for persons as free moral agents, (2) concern to support the best interests of human subjects in research, and (3) interest in assuring that the use of human subjects in experimentation will on the sum redound to the benefit of society, appear in various fashions in the literature and codes concerning human experimentation. When comparing the Nuremberg Code, the Declaration of Helsinki, the Department of Health, Education and Welfare rules and regulations for

the Protection of Human Subjects, and the Ethical Principles in the Conduct of Research with Human Participants of the American Psychological Association, one finds each of these three principles, though in various and often mixed forms.

A. Respect for human subjects as free agents:

The Nuremberg Code: "1. The voluntary consent of the human subject is absolutely essential."¹⁴

Declaration of Helsinki: "III. 3a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed."¹⁵

DHEW Regulations: "'Informed consent' means the knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion."¹⁶

American Psychological Association: "3. Ethical practice requires the investigator to inform the participant of all features of the research that reasonably might be expected to influence willingness to participate and to explain all other aspects of the research about which the participant inquires. ... 4. Openness and honesty are essential characteristics of the relationship between investigator and research participant. ... 5. Ethical research practice requires the investigator to respect the individual's freedom

to decline to participate in research or to discontinue participation at any time."¹⁷

B. Concern to foster the best interest of the individual human subjects:

The Nuremberg Code: "4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury. 5. No experiment should be conducted where there is a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subject. ... 7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death. ... 10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental patient."¹⁸

Declaration of Helsinki: "II. 2. The doctor can combine clinical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that clinical research is justified by its

therapeutic value for the patient."¹⁹ "In the purely scientific application of clinical research carried out on a human being it is the duty of the doctor to remain the protector of the life and health of that person on whom clinical research is being carried out."²⁰

DHEW Regulations: "It is essential that the committee, representing a wide spectrum of those expert professional skills essential to a clear recognition of an activity's inherent risks and probable benefits, carefully weigh such risks and benefits before determining that the benefits favor a decision to allow the subject to accept these risks."²¹ (My emphasis). This implies that volunteers should not be allowed to choose what the committee held was not in their best interests.

American Psychological Association: "7. The ethical investigator protects participants from physical and mental discomfort, harm, and danger. If the risk of such consequences exists, the investigator is required to inform the participant of that fact, secure consent before proceeding, and take all possible measures to minimize distress. A research procedure may not be used if it is likely to cause serious and lasting harm to participants."²²

- C. Concern to maximize the benefits accruable to society from research involving human subjects:

The Nuremberg Code: "2. The experiment should be such

as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature. ... 6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment."²³

Declaration of Helsinki: "I. 3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject. 4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others."²⁴

DHEW Regulations: "The risks to the subject [must be] outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks."²⁵ (My emphasis).

American Psychological Association: "Where scientific or humane values justify delaying or withholding information the investigator acquires a special responsibility to assure that there are no damaging consequences for the participant."²⁶

Even in the above excerpts which are chosen to highlight each principle in turn, there is often a simultaneous appeal to one or both of the other two principles. This must stem in part from the ways it is in fact

useful to establish procedural maxims for ethical conduct in human experimentation. For example, free and informed consent functions not only as a means of ensuring respect for persons, but as a way to pursue other values such as having a society in which one would not live in fear. It is therefore useful to reformulate the three basic ethical principles under procedural maxims. Particular maxims often involve the application of one of the three ethical principles in a restricted context. They often as well combine more than one principle under a single procedural maxim because one human activity (e.g., gaining free and informed consent) can serve more than one purpose.

The basic procedural issues can be clustered under four headings: (1) obtaining the free and informed consent of the human subject involved in the research under consideration; (2) obtaining a proxy consent from individuals unable to consent in order to protect the best interests of those subjects; (3) avoiding coercion which would unduly direct by threat the consent of a human subject (i.e., one can be said to have chosen in a free--e.g., while not drugged--and informed fashion to give one's money to a mugger under threat in the sense that one is a free agent and may be informed clearly of the consequences of not handing over one's money, though one cannot be said to have done it voluntarily). There is, in short, a distinction to be drawn between the freedom of moral agents versus the liberty of uncoerced agents (compare the contrast between the freedom of a normal adult versus its absence in a three-year-old child, and the contrast between the liberty of choosing without coercion versus under duress). Thus, infants cannot give free consent, normal adults can give free consent, though the consent of

some normal adults, perhaps prisoners, may not be voluntary; (4) one ought to weigh the benefits versus the risks involved in the use of human subjects in research in order to be assured that the costs of such research will not outweigh its possible benefits. This procedural principle is a nearly perfect reiteration of the moral principle (C) above to maximize the benefits accruable to society from research involving human subjects. It is the most clearly teleologically-oriented procedural principle.

Because the four procedural principles outlined above reflect divergent moral considerations, it is worth laying them out schematically to show the diversity of issues at stake:

- A. One ought to acquire the free and informed consent of human subjects involved in biomedical or behavioral research. Such a maxim can be seen to be derived from at least three origins:
 - a. Respect for the person-subjects as moral agents (ethical principle A).
 - b. Interest in encouraging autonomy as a general social value (ethical principle C).
 - c. Concern to ensure that the best interests of the subject can be secured (ethical principle B).
- B. When true consent cannot be acquired because the subject is not a moral agent (e.g., is an infant), proxy consent should be obtained:
 - a. To ensure that the best interests of human subjects will be considered (ethical principle B) within the

bounds of (i) the general duty of human subjects to assist their society in recompense for benefits received or likely to be received (a type of covenant obligation that would be derived from respect of the other members of society in principle A); (ii) to preserve the general social interest in autonomy by rehearsing a ritual of free and informed consent on behalf of the human subject to be involved in research, although that subject cannot consent on his/her own behalf (ethical principle C); (iii) a concern to preserve care and fellow feeling towards human subjects, even those subjects not capable of acting freely, because of our interest in those sentiments (ethical principle C).

b. To establish a means to ensure that human subjects who will become free agents will not have their existence and abilities compromised before they can act freely concerning their own lives (i.e., children who will be moral agents and suffer the results of past care--ethical principle A).²⁷

C. One should avoid coercion of persons who are considering volunteering as subjects in research, in order:

- a. To preserve respect for persons (ethical principle A).
- b. To increase autonomy in society, a goal of general interest (ethical principle C).

- D. One should weigh benefits versus risks in order:
- a. To ensure that the benefits to subjects involved in therapeutic experimentation outweigh the risks to those subjects (ethical principle B). This can be a paternalistic concern which would foreclose a patient's ability to pursue an experimental form of therapy which a disinterested observer might not find justified considering the unlikelihood of success and the amount of discomfort, or it can be a concern to maximize utility.
 - b. To ensure that the benefits to society justify the risk to the individual involved in non-therapeutic experimentation (ethical principle C). This may also involve paternalistic considerations (and thus ethical principle B)--a volunteer may wish to risk his or her welfare by agreeing to participate in an interesting and risky experiment with only remote chances of revealing significant information, and which would not in the eyes of a disinterested observer be a justified risk.

As indicated by the points outlined above under each of the four procedural principles, the considerations are diverse and turn on issues from the respect of the freedom of persons to considerations with regard to protecting or advancing certain goods and values.

III. OPINIONS IN THE CURRENT LITERATURE CONCERNING BASIC ETHICAL PRINCIPLES WHICH SHOULD GUIDE THE USE OF HUMAN SUBJECTS IN BIOMEDICAL AND BEHAVIORAL RESEARCH

The literature concerning the use of human subjects in experimentation is immense, but relatively little of it bears on the question of basic ethical principles. What does, does so somewhat unsystematically. As a consequence, what I will provide here is a typology of the various positions arrayed according to the schemata of the ethical principles and procedural maxims outlined above. In doing this, a few authors are presented in order to cluster the issues around particular viewpoints concerning the nature of the basic ethical principles involved in the use of human subjects. The authors and materials have been chosen in order to display the range of ideas with some clarity, rather than to give an inventory of the authors writing on this subject.

A. The Role of Consent by the Human Subject

The concern for informed consent by the human subject involved in research is clearly drawn from a sense of responsibility to respect persons as moral agents by never treating them as means merely, but rather as entities who have a right to their own self-determination. A very thorough examination of the moral significance of consent is provided by Charles Fried in Medical Experimentation. He begins from the legal intentions that only consent which is free and informed "justifies what the law calls 'intermeddling' with a person's body."²⁸ Out of this moral position in the fabric of the law, Fried argues to four moral rubrics which focus on medical procedures, including experimentation with human subjects: (1)

lucidity, (2) autonomy, (3) fidelity, and (4) humanity. By lucidity, Charles Fried means that "the patient [but for that matter the subject in research as well] has a right to know all relevant details about the situation he finds himself in."²⁹ This is an accent on knowledge sufficient to rational action. By autonomy, Fried means the "liberty to dispose of one's self, that is, of one's person, one's body, mind and capacities according to a plan and a conception fully chosen for one's self."³⁰ In his appeals to fidelity, Fried wishes to exclude lying or deceit, and under the rubric "humanity" he wishes to hold that "a person has a right to have his full human particularity taken into account by those who do enter into relations with him"³¹

In all of these, Fried appears to be developing basic deontological considerations in the context of research involving human subjects. His position is very close to the Kantian categorical imperative that persons "be treated at all times also as ends-in-themselves [i.e., as free agents], never merely as means."³² This is not to say that Fried examines the issues of individual rights to the neglect of social duties. He is very clear that one of the central concerns with the morality of experimentation is the extent to which the bodies of persons "are at the disposal of the human groups of which they are a part."³³ He suggests in fact that the right to receive medical care may be bound to a duty in at least some circumstances to contribute as a subject to biomedical research.³⁴ His accent, though, is upon the rights of individuals to their own integrity, including the integrity of their bodies and the right to be treated with honesty.

The value of informed consent, along with its function as a moral imperative for treating persons with respect, is outlined in a useful but different fashion by Alexander Capron. He lists the functions of consent as (1) to promote individual autonomy; (2) to protect the patient-subject status as a human being; (3) to avoid fraud and duress; (4) to encourage self-scrutiny by the physician-investigator; (5) to foster rational decision-making; and (6) to involve the public.³⁵ His first consideration, to promote individual autonomy, is the most clearly deontological, focusing on the duty to treat human subjects with respect. And the second point, to protect the patient-subject status as a human being, appears to be a further development of this first point, while the third point, to avoid fraud and duress, involves for Capron, sketching out procedures to protect the subject's freedom from the zeal of the investigator. Thus, in the first three cases, Capron emphasizes respect for the human subject as a free agent and involves a reiteration of Fried's points with respect to lucidity, autonomy, and fidelity.

His fourth point, to encourage self-scrutiny by the physician-investigator, is a procedural consideration intended to provide a useful inventory of the risks involved in the research, as well as to promote candor by the investigator to aid patients to distinguish between those elements of an intervention which are therapeutically-oriented and those which are bent on research alone. The fifth point, to foster rational decision-making, is a further iteration of the fourth point with the accent falling on making the human subject a better partner in the research in which he or she participates. Finally, the sixth point, making the issues involved in the free and informed consent explicit so that the public can make better judgments con-

cerning the probity of particular research, involves both a general interest in promoting autonomy as a general social value (an aspect of points four and five), as well as other general social interests, including social control of the kind and quality of research.

To borrow a phrase made popular by Paul Ramsey, analyses such as those by Fried and Capron concern how to treat the human subject in research as a person, considering both to the duty to respect human subjects as free moral agents, and the concern to maximize a general social value, that of autonomy. One should notice, though, that these are two quite different concerns. The first bears on maintaining the relationship between investigator and subject as a moral one, as a partnership or a covenant between subject and investigator. As Ramsey puts it, "consent expresses or establishes this relationship [i.e., between subject and investigator as persons], and the requirement of consent sustains it. Fidelity is the bond between consenting man and consenting man in these procedures."³⁶ The second is a concern to promote autonomy as a value, apart from any consideration of autonomy as a basic right. Consider Professor Hans Jonas' remark that "the individual's interest in his own inviolability is itself of public interest such that is publicly condoned violation, irrespective of numbers, violates the interest of all. In that case, its protection in each instance would be a paramount interest, and the comparison of numbers would not avail."³⁷ There is, as well, a third consideration, that allowing the individual subject free and informed consent increases the likelihood that the choice will be in the interest of that subject, on the presupposition that that subject is the best judge of his or her own best

interests. With respect to basic ethical principles, this consideration is often reducible to either ethical principle A or ethical principle C, namely, respect for persons or maximizing the general good in society through individual initiative. Also, informed consent may derive from enlightened self interest, a concern to allow others to choose in their best interests so that we may similarly have that prerogative. Further, some have argued that informed consent is justified in part because of the feeling of well-being it gives to the volunteer. "It appears to this writer [John Fletcher] that the conduct of the consent situation is decisive for the patient's or volunteer's sense of being respected as a person, especially when the request is for a procedure which is non-beneficial."³⁸

In contrast to the arguments concerning the necessity of free and informed consent, there is as well a set of arguments alleging the impossibility of free and informed consent: "The subject is ordinarily not qualified to evaluate the true risks and expected benefits of any experimental drug or procedure. In addition, an investigator who is eager to confirm some hypothesis might, in informing the subject, minimize, either consciously or unconsciously, experimental risks and uncertainties. Indeed, the investigator may not know all the risks. ... "³⁹ Such arguments cannot be taken seriously without eroding the very possibility of recognizing free choice in society generally. Persons, though never acting in any case as perfectly free and rational agents, do so up to a point. The attempt to achieve informed consent provides a criterion for moral action in the use of human subjects. It provides one with a moral maxim: one should provide all the facts material to a subject's decision (including the extent to which facts

or good information does not exist), and give that subject an opportunity to acquire further facts to the point at which that subject is satisfied with his or her understanding of the research at hand. And, again, the absence of good information concerning some possible outcome of the experiment can also be conveyed. (Laymen come into situations of incomplete or minimal information more often than scientists assume--consider visits to auto mechanics, or farmers judging next year's crop.)

To this must be added that third parties should ensure that the important risks and issues at stake are brought to the subject's attention--a function at present served by DHEW mandated committees. One cannot try (nor should one) to force subjects who can be rational free agents to use that rationality and freedom to its fullest. Informed consent means that the investigator should not circumscribe the free and rational character of the subject's choice, but rather support that character as far as possible. The concept of informed consent thus functions to guarantee that researchers will not act in disregard of their subjects as persons. It cannot, however, function to guarantee that subjects will be ideal moral agents who will act on their choices in a fully free and informed fashion. It is only that the deficiency in their choice should not be attributable to the investigator.

Informed consent as a means of preserving the interest of persons against the interests of researchers in using them functions best through the protection of formal review committees. One should not conclude with Dr. Inglefinger that "the process of obtaining 'informed consent' ... is no more than

an elaborate ritual ... " because investigators can usually extract consent.⁴⁰ Rather, one should conclude that better public education and public safeguards should be provided in order to support the free and informed consent of subjects, and to avoid coercion in the obtaining of such consent.

However, a special set of experiments do require some level of deception and, therefore, some restriction of free and informed consent in order to make them possible. These usually include randomized clinical trials of drugs in which neither the investigator nor the patient knows whether the patient is receiving a standard drug and/or a second drug and/or placebo used in comparison. From the argument above, it would follow that one would owe to the patient (1) clear knowledge that he or she was the subject of a randomized clinical trial (i.e., might be receiving, for example, a placebo or a less well-known drug); (2) assurance that there was good evidence that being subjected to this risk of receiving a non-standard drug or placebo would not be a substantial risk to the patient (a proper paternalistic concern); and that (3) provision was made to evaluate the difference between the therapies so that should one therapy show itself to have a particular advantage or a particular risk, further trials would be discontinued. One needs, in short, to meet two central moral issues involved in randomized clinical trials for, to quote Charles Fried, "The protocol may require an abdication of professional judgment such that the patient's therapy is determined not by the needs of his particular case, but by the demands of the experimental design," and "The practice of RCT's [randomized clinical trials] often, though not necessarily, involves deceit."⁴¹ Given a full disclosure of the facts of the trial, and given a careful assessment that

a random clinical trial is merited because of the uncertainty with respect to the merit of the treatment or treatments currently available, there are not insuperable problems. Individuals can be given sufficient information so that they can decide to assume a minor risk for the acquisition of medical knowledge. One is thus brought back to the basic ethical principle A, to treat the subject with respect, and basic principle B, to protect his or her best interests. Though consent in the contexts of research rarely possesses the clarity to justify the maxim "Volenti non fit iniuria," it is rarely so muddled or invincibly in the dark that a proper presentation of information will not allow a morally adequate choice.

There is though, a genre of experiments which depends necessarily upon an element of deception--usually experiments in psychology or social psychology. They are often innocuous studies in which the only violence done to the subject is being told a lie concerning the actual aim or goal of the research.⁴² Others have included substantial psychological, as well as moral, risks. Some of these experiments have indeed provided varying degrees of informed consent. For example, Professor Philip G. Zimbardo, in reflecting on critiques of his Stanford prison experiment, states that "the 'informed consent' statement, signed by every participant, specified there would be an invasion of privacy, loss of some civil rights and harassment."⁴³ Experiments such as Stanley Milgram's have involved subjects in circumstances with both an element of deception and of risk.⁴⁴ Subjects were asked, for example, to apply electroshock to a second person, in a controlled social setting (under the ruse of participating in a scientific experiment).⁴⁵ One should note that there is not only a psychological risk, but a moral one as well--

the subject may, in such experiments, be caused to perform an action which he or she would hold to be immoral. That is, a psychological experiment can function as a form of seduction with not only psychological but ethical consequences for the subject involved. Experiments should not be designed which would entice persons to violate moral maxims, because to do so is to fail to treat the subject as a moral agent, as worthy of respect. One fails to acknowledge the subject's moral integrity.

It is worth noting that The Ethical Principles in the Conduct of Research with Human Participants of the American Psychological Association provides for deception if the researcher shoulders the moral responsibility of that deception. For example, "Failure to make full disclosure gives added emphasis to the investigator's responsibility to protect the welfare and dignity of the research participant. ... The decision to limit this freedom [i.e., to decline to participate in research or to discontinue participation at any time] increases the investigator's responsibility to protect the participant's dignity and welfare."⁴⁶

There are at least three issues at stake with respect to free and informed consent in such research: (1) whether active deception is permissible--whether researchers have a right to lie in the service of science; (2) whether researchers have a duty to disclose the nature of a psychological experiment, if an experiment has the possibility of attendant risks, even in the absence of active deception; (3) whether in the absence of active deception, or with a degree of deception not materially different from that of everyday social interactions (e.g., polite evasion of the truth), an investigator has a duty

to disclose the nature of an experiment when no risks to that subject, including invasion of privacy, are involved.

Respect for persons, it would appear, precludes any active deception in the performance of an experiment. Persons as such have a right not to be used as means merely. But, depending on the nature of the experiment, it may at times be possible to inform subjects that they will be set at risk of some deception, and thus avoid using them as means merely, while still avoiding disclosing the particular variables under study.⁴⁷ In some cases, then, when the risk is minimal, general consent can be reasonably given to a risk of some deception as part of an experiment protocol. The crucial moral issue is that there not be greater deception, nor greater risk of psychological or ethical harm, than the subject would have anticipated in his or her consent, and that that risk, in any event, not be substantial. Beyond that, deception which one has accepted should be considered as morally harmless, as is the systematic deception which is part of a well-played game of poker.

There should be, as well, a recognition of the right of the subjects not only to be free of active unaccepted deception, but there should be disclosure of relevant information when an experiment sets that subject at risk, even in the absence of deception. It is incompatible with respect for persons as free moral agents to set them at a risk without their consent, for such action would be a paradigm case of using another as a means merely, as an object rather than as another person. The only circumstances which might be exceptions to this rule would be those in which the research was

to the direct benefit of the recipient and the experimental nature of the procedure was not relevant to the patient's choice. One might be able to conceive of cases in which an experimental therapy is the treatment of choice for a patient with a serious disease, and the patient is in circumstances such that a full disclosure of the nature of the therapy would worsen the patient's prognosis.⁴⁸ Those cases are probably very rare. Moreover, physician-experimenters would be morally justified in withholding such knowledge only when they were sure that the patient would indeed want to pursue such therapy. After all, patients have a moral right, and an increasingly recognized legal right, to refuse therapy, including life-saving therapy. Such decisions would have to be made with every reason to believe that one would not be acting against the choice of the patient.

Finally, there is a class of experiments which involves neither risk nor intrusion, but simply observation. The American Psychological Association gives the example of observing transportation patterns or other forms of natural public behavior which are, in any event, open to everyone's critical observation.⁴⁹ Though the researcher does not have any rights beyond those of the normal citizen to lie and deceive, the researcher does not have a special obligation to make known his or her projects to others if those projects are non-invasive and carry no risk to the subjects involved, apart from the general risks of everyday life (e.g., being observed while doing what people usually do on the public streets). Such research could reasonably include that element of deception which is part of everyday life --the researcher may hold a job as a part of a research endeavor in order to better observe worker interaction, without divulging to the workers in

advance his true identity.⁵⁰ That is, one can presume that people consent to a minimal level of disingenuous behavior as an element of public life (e.g., no one tells the host that his choice of wine is poor). The line between harmless passive deception of others which is part of usual life situations (i.e., hiding elements of one's true thoughts, etc.) versus active deception of an active fashion that departs from this level, is, as are all lines in real life, difficult to draw.

All these concerns coalesce around the three points raised under the procedural maxim of obtaining free and informed consent of human subjects participating in biomedical and behavioral research. Respect for human subjects as persons requires gaining their free and informed consent in order to use them, not as mere objects, but as collaborating persons in an experiment. The exceptions are those where in fact no use is made of another-- research involving only the observation of everyday deportment (where consent to observe is implied in the very act of entering a publicly observable sector of the world). And, again, the other roles of consent must be emphasized: to encourage autonomy as a general social value, and to ensure that the best interests of the subject are secured.

B. The Role of Proxy Consent

One of the most contested issues concerning experimentation involving human subjects is the role of proxy consent. It is surely a strange notion-- something like having a friend drink a glass of water for you when you are thirsty. If consent functions as a way of respecting the freedom of individuals by gaining their leave in order to use them in research, then proxy

consent rarely makes sense (it would in cases where individuals have indeed enacted a power of attorney in order to convey to others the right to make decisions on their behalf while they are incapacitated).

A number of individuals have on the basis of respect for persons argued against the concept of proxy consent. Paul Ramsey, for example, would allow proxy consent only in cases where such consent is made on behalf of the manifest good of the individual concerned--for example, a parent consenting to therapeutic experimentation, with the prime intention of choosing the form of therapy most likely to be of use to the child. To quote Ramsey, "From consent as a canon of loyalty in medical practice it follows that children, who cannot give a mature and informed consent, or adult incompetents, should not be made the subjects of medical experimentation unless, other remedies having failed to relieve their grave illness, it is reasonable to believe that the administration of a drug as yet untested or insufficiently tested on human beings, or the performance of an untried operation, may further the patient's own recovery ... consent-requirement means: 'Never submit children to medical investigation not related to their own treatment, except in face of epidemic conditions endangering also each individual child.'⁵¹ Ramsey's objection is based on the contention that to make a child subject to an experiment involving any risk or discomfort is to use that child as a means merely, rather than acknowledging it with the respect due to persons.

In short, Ramsey's argument is that one should treat all humans the same, and, since one treats adult humans with respect due to free agents, one should do the same with respect to infants. He puts this very strongly, "[children] can be harmfully used, or they can simply be used with no harm.

Both the degradation of the body's fortress and being treated as a means only are human violations."⁵² This position would exclude children from any non-therapeutic research, except passive observation involving no touching or other intrusion. Ramsey's position evidently is meant to apply to all humans who might be incapacitated, and precluded from giving free and informed consent.

The preponderance of those engaged in biomedical and behavioral research appear to accept more readily using infants and other incompetents. Though the Nuremberg Code omits mention of the use of incompetents, provision for this is explicitly made in the Declaration of Helsinki ("If he is legally incompetent the consent of the legal guardian should be obtained").⁵³ Curran and Beecher must be counted in this group. They have argued for allowing research involving immature children (those under fourteen years of age) when there is no discernible risk. "Not to allow such studies would greatly hamper important nutritional, psychological, and educational studies in children, as well as studies of inborn errors of metabolism and genetic defects."⁵⁴ That is, there are special issues raised concerning the physiological and psychological responses of children and the mentally ill that can only be answered by research involving these populations.

Moreover, treatment tried for the first time in special populations (e.g., children) constitutes an experiment. As Leon Eisenberg points out "There is a non-trivial risk whenever a drug is given for the first time to a child. Further, the more potent the drug in treating the condition at which it is directed, the greater the risk of undesired side-effects."⁵⁵

Such experimentation is particularly troublesome when, as in the case of the rubella vaccine, its prime intention was not to prevent rubella in the children vaccinated, but in the fetuses which some of those children might bear. To encompass experimentation such as the trial of the rubella vaccine, one would not only have to allow intrusive experimentation on incompetent populations redounding the benefit of that population (e.g., aiding in the development of treatment of childhood diseases or mental illnesses), but would also have to include research that cannot be done in other populations (e.g., use of rubella vaccine in pediatric age populations would always be, at the time of its first introduction, experimental--and insofar as the major goal would be to prevent fetal defects, it would to that extent not be for the benefit of the population of children.⁵⁶ In order to have a rubric to encompass all such experimentation on children and other incompetents, one would need a rule somewhat similar to that forwarded by the AMA, that "minors or mentally incompetent persons may be used as subjects only if: (1) the nature of the investigation is such that mentally competent adults would not be suitable subjects; (2) Consent, in writing, is given by a legally authorized representative of the subject under circumstances in which an informed and prudent adult would reasonably be expected to volunteer himself or his child as a subject."⁵⁷ One would, in short, have to have a rule which sanctioned experimentation on incompetents, when that experimentation was non-therapeutic and involved very minimal risks and discomforts.

There have been several attempts to resolve the problem of the use in research of incompetents and, in particular, children. Suggestions have been

made of a procedural sort, namely, that one should move progressively into younger age groups, thus avoiding any very unexpected reactions in the introduction of new drugs.⁵⁸ On the other hand, Richard McCormick has attempted to give a solution in principle. He wishes to justify those experiments involving children "that are scientifically well-designed (and therefore offer hope of genuine benefit), that cannot succeed unless children are used ... [and] that contain no discernible risk or undue discomfort for the child."⁵⁹ McCormick's position thus contrasts with Paul Ramsey's, for McCormick would allow subjecting children to discomfort. McCormick justifies such use (*i.e.*, subjection to discomfort) of the child on the basis of what the child ought to wish to do. "To share in the general effort and burden of health maintenance and disease control is part of our flourishing and growth as humans. To the extent that it is good for all of us to share this burden, we all ought to do so. And to the extent that we ought to do so, it is a reasonable construction or presumption of our wishes to say that we would do so ... sharing in the common burden of progress in medicine constitutes an individual good for us all up to a point."⁶⁰ It is in this fashion that McCormick justifies extensive experimentation and research upon children which is morally foreclosed according to Ramsey's account.

Both Paul Ramsey and Richard McCormick frame their arguments as if one had to consider the will or wishes of incompetents. Yet, it is precise because incompetents have no will, in the sense of a moral will, that they are incompetent, they cannot choose. There is, thus, no contradiction between the AMA's statement that minors and mentally incompetent persons can be used in research on the basis of proxy consent, and the assertion

that "no person may be used as a subject against his will."⁶¹ One does not violate the will of a baby as one brings it kicking and screaming to a harmless pin prick as its sole contribution to a hematologist's study of small infants. There is no one's will or freedom to violate. Infants, though often willful, have no free will, and are not the object of respect in the sense that adults are. Thus, one respects the right of a Werner Forsmann to catheterize his own heart⁶² at unknown and, perhaps, considerable risk, while one does not accept the free consent of a normal three-year-old child to similarly volunteer itself. Proxy consent does not exist to respect the child as a moral agent, but rather to safeguard its best interests.

If proxy consent is not seen as a safeguard against the violation of an infant's wishes (on the grounds that it is not a free agent as normal adults are), but rather as a means to protect its best interests, it follows that that experimentation that does not involve an increase of risk over the ambient or any significant discomfort, should be allowed. One is not violating anyone's moral integrity. The point is rather to preserve the physical and psychological integrity of the child. Experiments that do not set the physical or psychological integrity of the child, or other incompetents, at risk should be prima facie allowable.

McCormick's point can then be reformulated, not in terms of what the child ought to wish, but in terms of what minor increase in risks should reasonably be borne by us all as members of a society that has chosen to pursue certain goals, including the improvement of health care without

appearing severe or undue.⁶³ This final issue is too complex for the scope of this paper. The most that can be indicated is that nearly all societies recognize a certain minimal level of risk as a social obligation to which one may be said to have implicitly consented by one's presence. Of course if they were competent, the children might protest, even to the point of demanding exit from the society. But insofar as they are not, they are not bearers of freedom, and need not be respected. They are though bearers of interests, and therefore to be cared for. Thus, proxy consent functions not as a way of respecting incompetents as moral agents, but as a way of protecting their best interests. Therefore, experiments that would not act against their interests, by exposing them to physical or social psychological risks, greater than those in the usual ambiance, are prima facie proper. Experiments involving very minimal risks (nearly that of the subject's ambiance) and minor discomfort, should be justifiable in terms of an appeal to the minimal duties that each of us owe to our society. There will, in the second case, surely be no clear lines to be drawn. One would hope that such lines will be drawn by prudent persons. But the absence of black and white distinctions should not cause one to retreat into the darkness, rather than to attempt to draw reasonable lines in the twilight.

C. Avoiding Coercion in the Context of Research

The issue of coercion in research involving human subjects usually involves special populations such as students who may feel forced by their teachers to volunteer, prisoners who may feel coerced to volunteer because of their circumstances, or the poor who may be forced to volunteer because of the situations in which they receive their health care. I will not deal

with the issues of these special populations, except to make this point: the morality of the coercion brought to bear upon such populations cannot be assessed except in terms of very basic judgments bearing on the morality of the situations in which those populations live. It is thus not possible to decide whether prisoners should usually be barred from participating in non-therapeutic research, until one has decided what is due prisoners. One must first answer certain basic questions regarding the theory of punishment. Hans Jonas raises this issue in a very jarring fashion, "If we hold to some idea of guilt, and to the supposition that our judicial system is not entirely at fault, [prison inmates] may be held to stand in a special debt to society, and their offer to serve--from whatever motive--may be accepted with a minimum of qualms as a means of reparation."⁶⁴ Apart from whatever judgment one might have concerning Professor Jonas' statement, an adequate account of the use of prisoners must include an account of the role or rationale of the practice of punishment--and that lies beyond the scope of this paper.

In any event, action to prevent coercion in the procurement of consent to research is motivated out of respect for the integrity of persons as well as a concern to preserve autonomy as a value in society. Both issues, for example, appear in the Kaimowitz v. Doe case where the court held that "involuntary confined patients cannot reason as equals with doctors and administrators over whether they should undergo surgery. They are not able to voluntarily give informed consent because of the inherent inequality in their position."⁶⁵ One sees in such cases an attempt to discern the geography of offers and threats in order to distinguish between proper inducements to participate in research (e.g., satisfaction of contributing to science,

performing a socially approved act, making retribution for one's previous crimes, etc.), and those inducements which the Nuremberg Code indicated under the rubric of "duress, overreaching, or other ulterior form of constraint or coercion."⁶⁶ That distinction must be drawn on a case by case basis in order to prevent both coercion and foreclosure of free choice out of an inordinate fear that coercion is present. Coercion is an evil in the context of research because it bears both against the freedom of the subject as well as against the good of society. But an overzealous attempt to avoid the possibility of coercion (e.g., by categorically forbidding all non-therapeutic research with prisoners which does not bear directly on the good of prison populations) may deprive individuals of that very liberty one wished to protect. The issues here (apart from basic questions of the nature of punishment) are, for the most part, procedural rather than questions bearing on basic ethical principles.

D. Sufficient Benefits to Justify the Risk

It is not vicious, but in fact virtuous to attempt to maximize the goods available to us all. A utilitarian calculus set within the bounds of respect for persons as free agents can be a noble way of living in a world defined by scarce resources. One should not invest human resources and energies to no avail. This virtue becomes a duty in the use of public funds. Such considerations apply a fortiori to biomedical and behavioral research involving human subjects.

It is under this rubric of cost/benefit analysis that conflicts between individual versus societal rights have a natural place. They arise because

a society will be tempted to pursue experiments that promise considerable benefit at the cost of damage only to a few members of society, perhaps individuals already in a socially disadvantaged position. Those who lean toward the utilitarian viewpoint emphasize the benefits to mankind of human experimentation and are sometimes willing to suggest that the benefits of such research are so enormous as to constrain us to recognize a "duty" of subjects to participate in it. At the very least, what the utilitarian sees is a calculus of goods and values. As it was succinctly put by a contemporary writer, "Human experimentation is required in order for medical progress to be made. Such research will of necessity involve risks that can be minimized, but not eliminated. ... The problem, therefore, boils down to a sober weighing of costs and gains. ... "67

Balancing the expected good to result from research against the risk to the individual subject is, though, an ambiguous undertaking. It can have at least three meanings: (1) it can simply indicate a cost/benefit analysis for society in which one measures the good that would accrue to society from that research against the loss to society as a result of any damage to the individuals participating. That is a proper calculus, if placed within the bounds of respect for human freedom. A society may thus decide not to support research which on the balance would be costly to it, even if there were individuals free and willing to volunteer for it; (2) there is also the sense of balancing the expected benefit to the individual from the research against the foreseeable risks to the individual--an element of giving sufficient information for adequate consent to a subject considering entering a therapeutic experiment; (3) finally, society may

have a basis for forbidding individuals from participating in research with high potential risks and low potential yield. From paternalistic motives to act in the best interests of the would-be subject on the assumption that society, or some other organ of society, knows the best interests of that individual better than the individual, him or herself. But the difficulty with free agents, as indicated above, is that the defining characteristic, upon which the moral significance of values hinges, is to act freely. Therefore, it may be one thing to decide not to support such research through public funds, and another thing to try to prevent it through any other coercive methods. An element of a free society would seem to be that one can either jump motorcycles over gorges to fame, or participate in reckless experiments as long as the rights of others are not materially affected.

This last point, thus, concerns balancing goods within the bounds of respect for freedom. Since we both respect persons and have interest in goods and values, we must allocate scarce resources as best we can to forward our commonly embraced goals within the bounds of never treating other persons as means merely. One may never treat others as means merely. But, one may, within the bounds of moral probity, treat others as means. Informed consent of the other one is the difference between using another as a means, and using another as a means merely. Which is to say, ethical principles (B) and (C), bearing on the best interests of individual subjects and the best interests of society, find their locus within the bounds of respect for human subjects as free agents (principle A). In the end, what distinguishes the moral problem of experimentation with human subjects from the moral problems of experimentation with subjects of other species, is that only persons can make absolute claims to respect.

IV. SUMMARY

Moral postures concerning research involving human subjects are diverse in part because of the diversity of issues at stake in, for example, disputes over conflicts of rights and duties, concerning values, and with regard to duties to persons with interests in goods and values. I have presented three ethical principles around which to gather these questions: (1) respect for human subjects as free agents; (2) concern to foster the best interests of human subjects; and (3) concern to maximize the benefits accruable to society. I have indicated that these three abstract considerations arise around four procedural foci for research involving humans: (1) the requirement of free and informed consent of competent human subjects; (2) the requirement of proxy consent from incompetent human subjects; (3) the avoidance of coercion in the consent context; and (4) an interest in having research involving humans redound to the general good of society. These are at best guidelines, or outlines of the central ethical issues at stake. They must in each case of research be applied with care and followed with prudence. One can never have a means of simply deducing answers. Basic ethical principles represent, rather, our best attempt to map out the terrain of rights and values.

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FOOTNOTES

1. These two questions can be distinguished as deontological versus teleological moral considerations, that is, concerns with rights and duties versus goals. As John Rawls succinctly puts it, "The two main concepts of ethics are those of the right and the good ... a deontological theory [is one] that either does not specify the good independently from the right, or does not interpret the right as maximizing the good. ... Now it seems that the simplest way of relating them is taken by teleological theories: the good is defined independently from the right, and then the right is defined as that which maximizes the good." A Theory of Justice (Cambridge, Mass., 1971), pp. 24, 30, 24.
2. Consider, for example, the attitudes of behaviorists, who interpret behaviorist psychology not as a methodology but as a form of metaphysics. See B. F. Skinner, Beyond Freedom and Dignity (New York, 1971).
3. What I am proposing here is a view of freedom and morality that draws heavily upon Immanuel Kant, that freedom is a presupposition for both claims to knowledge and morality. See Immanuel Kant, Critique of Pure Reason, A 542=B 570 to A 558-B 586. Foundation of Metaphysics and Morals (Grundlegung der Metaphysik der sinnen), in Kantswerke, Akademik Textausgabe (Berlin, 1968), Vol. 4, pp. 446-447.
4. A reduction can be made of any position holding that persons are not free in this fashion: one could disagree with the proposition that persons are free only on the basis of presupposing that persons are free, that is, by presupposing that one choose to hold one's position (i.e., that persons are not free) on the basis of good reasons.
5. The Nuremberg Code, in CIOMS Round Tables, ed. V. Fattorusso (Paris, 1967), p. 100.
6. It follows that the fact that infants and other incompetents cannot be treated as persons in the same way that normal adults can, that humans are persons in different ways. Normal adult humans are persons in the strict sense of being actual moral agents, bearers of rights and duties. Small children and other mental incompetents are treated as if they were persons, moral agents, insofar as this is possible. That is, they are treated as having moral rights, but not moral duties (e.g., an infant can be said to have a right to life, but not a duty to preserve the lives of others). Moreover, though infants and other incompetents can be said to have rights to certain goods, they do not have a right to be treated as free moral agents, which

they are not. This distinction is of importance with respect to proxy consent, and Paul Ramsey's position which is discussed below.

7. In this regard, Kant offers the useful distinctions between the dignity of persons and the values of things. A person may be treated as having a particular value (e.g., a utility value), but must also be acknowledged as having the dignity of a free agent. A person has the right to be treated not merely as an object, but also as self-determining--an entity who can be used only with his or her consent. Metaphysik der sitten, in Akademik Textausgabe, Vol. 6, pp. 434-435.
8. In this sense a person has a right to be treated as a free agent in human research, not because treating him or her otherwise would erode the fabric of society, etc., but simply because that is what is due that human subject.
9. Talk about rights and duties also occurs within teleological theories of morality. In such contexts, it really stands for concern for some good or value. In such a framework, the subject's right to free and informed consent would express a judgment that in the absence of such a practice members of society might be put in jeopardy, feel ill at ease, etc. Such talk of rights and duties is a disguised way of talking about or enjoining one to action upon goods and values. Consider, for example, John Stuart Mill's treatment of the status of rights in Utilitarianism. "To have a right, then, is, I conceive, to have something which society ought to defend me in the possession of. If the objector goes on to ask why it ought, I can give him no other reason than general utility." Utilitarianism, ed. Oskar Piest (Indianapolis, 1957), p. 66. "... all cases of justice are also cases of expediency ..." (p. 79).
10. Note that here the interest in human autonomy is a teleological one, a good the pursuit of which has general social value.
11. That is, giving such respect to persons is a conceptual condition, part of what is required in talking about responsibility to persons as free agents. It is not a material condition, as, for example, regular adherence to a utilitarian rule is a condition for maintenance of a moral practice.
12. It is in this sense that respect for freedom is not a value, but the condition for the possibility of responsibility to persons as moral agents. But treating persons as free does not preclude making evaluations concerning persons in a utilitarian fashion, as long as such evaluation does not preclude respect for those persons as moral agents. E.g., one might not give persons the opportunity to consent to research of little benefit through precluding public funding of such research.

13. Arguments that the conditions under which prisoners are held prevents them from giving voluntary consent to any experimental procedures are relevant here. See, for example, Kaimowitz and Doe v. Department of Mental Health for the State of Michigan, Civil Action No. 73-19434-AW (1973). The ruling distinguishes among three elements of adequate consent: competency, knowledge, and voluntariness.
14. The Nuremberg Code, p. 100.
15. Declaration of Helsinki, in CIOMS Round Tables, p. 103.
16. "Department of Health, Education and Welfare Rules and Regulations: Protection of Human Subjects," Federal Register, 39 (May 30, 1974), p. 18917, § 46.3c.
17. American Psychological Association, Inc., Ethical Principles in the Conduct of Research with Human Participants (Washington, D.C., 1972), p. 1 f.
18. The Nuremberg Code, p. 100 f.
19. Declaration of Helsinki, p. 103.
20. Declaration of Helsinki, p. 103.
21. DHEW Rules and Regulations, p. 18914.
22. American Psychological Association, Inc., p. 2.
23. The Nuremberg Code, p. 100.
24. Declaration of Helsinki, p. 102.
25. DHEW Rules and Regulations, p. 18917, § 46.2. As the reader will note, this quote from the DHEW regulations is nearly the same in wording as the one under (B) above. Both quotes contain the accent on the best interests of the subject, as well as on the benefits accruable to society.
26. American Psychological Association, Inc., p. 2.
27. The duty to treat infants with care is thus greater than the duty to so treat incompetents such as the permanently and severely senile, because children will become free moral agents whose integrity as such will have been compromised by those who failed to give them due care. It is to persons in the strict sense, as free moral agents, that we owe the basic duty of moral respect.
28. Charles Fried, Medical Experimentation (New York, 1974), p. 19.
29. Fried, p. 101.

30. Fried, p. 102.
31. Fried, p. 103.
32. Kant, Grundlegung der Metaphysik der Sitten, in Kantswerke, Akademik Textausgabe (Berlin, 1968), Vol. 4, p. 429.
33. Fried, p. 4.
34. Fried, p. 157.
35. Alexander M. Capron, "Informed Consent in Catastrophic Disease, Research and Treatment," University of Pennsylvania Law Review, 123 (December, 1974), 364-376.
36. Paul Ramsey, The Patient as Person (New Haven, 1970), p. 5.
37. Hans Jonas, "Philosophical Reflections on Experimenting with Human Subjects," Daedalus, 98 (Spring, 1969), 222.
38. John Fletcher, "Human Experimentation: Ethics in the Consent Situation," Law and Contemporary Problems, 32 (Autumn, 1967), 632.
39. Robert D. Mulford, "Experimentation on Human Beings," Stanford Law Review, 20 (November, 1967), 106.
40. F. J. Inglefinger, "Informed (but Uneducated) Consent," New England Journal of Medicine, 287 (August 31, 1972), 466.
41. Charles Fried, Medical Experimentation, p. 148.
42. For example, see Jerome H. Resnick and Thomas Schwartz's discussion of an experiment in which a control group was told that the experiment's goal was to determine how college students form sentences, though the goal was to determine the effect of verbal reinforcement of certain words used by the subjects while doing the experiment. One group of these individuals was treated simply as controls (i.e., no further information was supplied); another group was told that they were indeed being employed in such an experiment. The real experiment was to find out whether telling the truth concerning the experiment would alter the results of the reinforcement of certain usages of language. It did. Cf. "Ethical Standards as an Independent Variable in Psychological Research," American Psychologist, 28 (1973), 134-139.
43. Philip G. Zimbardo, "On the Ethics of Intervention in Human Psychological Research: With Special Reference to the Stanford Prison Experiment," Cognition, 2 (1973), 243-256.
44. Milgram's subjects were paid \$4.50 for participating "no matter what happened." Yet, it is unlikely that they consented to being stressed

and some were apparently below the age of legal consent. It can also be argued that the researcher's motivation was altruistic, to contribute to recorded scientific knowledge. And valuable behavioral data were recorded--over 50% of the subjects continued to administer what they thought was full, actual shock, even after the confederate expressed great pain." Robert I. Gordon, "Mental Distress in Psychological Research," Baylor Law Review, 21 (1969), 526.

45. Stanley Milgram, "Some Conditions of Obedience and Disobedience to Authority," Human Relations, 18 (1965), 57-75. Reprinted in Jay Katz, Experimentation with Human Beings (Hartford, 1972), 358-365. "[In one variation] the victim received a shock only when his hand rested on a shock plate. At the 150-volt level, the victim again demanded to be let free and, in this condition, refused to place his hand on the shock plate. The experimenter ordered the naive subject to force the victim's hand onto the plate." Katz, p. 361.
46. Ethical Principles in the Conduct of Research with Human Participants, § 3, 5, pp. 1, 2.
47. One might ask whether classical studies such as those by Robert Rosenthal and Lenore Jacobsen (which involved deception of teachers as well as parents and students with respect to the intellectual abilities of those students in order to test how expectations influence performance) could have been performed had the teachers and parents been given a blanket warning that some sort of study was underway. Also, a crucial question at issue is whether there was indeed any risk to the students involved. That is, even if the teachers and parents would have been willing to agree to participate in an experiment of an undisclosed nature, the crucial issue would be whether there was minimal risk so that such a venture would have been justified. See Pygmalion in The Classroom (New York, 1968).
48. The Drug Amendment's Act of 1962 (Kefauver-Harris Bill) removes the need for consent to the use of investigational drug when physicians hold "in their professional judgment [that such disclosure would be] contrary to the best interests of such human beings." Section 505(i).
49. American Psychological Association, Inc., p. 30f.
50. American Psychological Association, Inc., p. 32.
51. Ramsey, The Patient as Person, p. 11 f.
52. Paul Ramsey, "The Ethics of a Cottage Industry in an Age of Community and Research Medicine," New England Journal of Medicine, 284 (April 1, 1971), 704.

53. Declaration of Helsinki, III, 3 a, p. 103.
54. William J. Curran and Henry K. Beecher, "Experimentation in Children," Journal of the American Medical Association, 210 (October 6, 1969), 83.
55. National Academy of Sciences, Experiments and Research with Humans: Values in Conflict (Washington, D.C., 1975), p. 97.
56. Someone might retort that such experimentation did redound to the benefit of the population of children, namely, those fetuses who would not be born deformed due to rubella, thanks to the immunizations. But fetuses are not quite the same as children, for among other things, women exposed to rubella have abortion as a means of preventing the birth of children who might be thus deformed. In a real sense, the control of rubella exists for the good of parents.
57. American Medical Association, Opinions and Reports of the Judicial Council (Chicago, Illinois, 1971), p. 12.
58. Alexander Capron, "Legal Considerations Affecting Clinical Pharmacological Studies in Children," Clinical Research, 21 (February, 1973), 141-150.
59. Richard A. McCormick, "Proxy Consent in the Experimental Situation," Perspectives in Biology and Medicine, 18 (August, 1974), 14.
60. McCormick, p. 12 f.
61. Judicial Council Opinions and Reports, p. 12. My arguments have involved children not capable of free choice--not older children who are and constitute a different and more complex problem. Children and other incompetents should be involved in all such decisions insofar as they are able.
62. Nobel Lectures, Physiology or Medicine, 1942-1962 (Amsterdam: Elsevier Publishing Company, 1964), p. 511.
63. An important critique of this position is given by Professor Hans Jonas, "Philosophical Reflections on Experimenting with Human Subjects," esp. p. 229 f.
64. Jonas, p. 246 n.
65. Kaimowitz v. Doe, p. 29.
66. Nuremberg Code, § 1, p. 100.
67. Louis Lasagna, "Special Subjects in Human Experimentation," Daedalus, 98 (Spring, 1969), 461.

9

MEDICAL ETHICS AND THE ARCHITECTURE OF
CLINICAL RESEARCH

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The current concerns over ethical issues in medical research arise at a time of unprecedented achievements in the research. Tuberculosis, poliomyelitis and other dread infectious diseases have become controlled or eliminated. Cardiac surgery, prosthetic joints, and renal transplantation or dialysis have transformed people's lives. Psychotropic drugs have dramatically improved the outlook for mental disturbance. These and many other advances in medical progress have made the continued conquest of human ailments become an expectation, not just a hope.

The clinical investigation that led to this progress, however, has recently come under intensive ethical scrutiny. Investigators have been castigated for alleged laxity in the conduct of the research, for occasional failure to attend to the basic rights of subjects, and for apparent exploitation of the poor, the ignorant, or the incarcerated. Unethical medical research has become a topic for deliberation by symposia of philosophers, attorneys and theologians; for prevention by institutional review committees; and for rejection by medical granting agencies and editors.

That medical research is necessary for medical progress has been uni-

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versally accepted. The main sources of current dispute have been not the need for research, but the kinds of research that are ethically permissible and the kinds of principles that distinguish ethical from unethical research. During the examination of these issues, the topic of human experimentation has often been regarded as a unitary activity, whose problems might be amenable to solution with such simple, single procedures as "informed consent."

Our purpose in this paper is to describe the complex intellectual architecture⁽⁴⁾ of projects in medical research, to indicate the diverse ethical problems⁽⁷⁾ raised by component elements of the architecture, and to suggest that many ethical issues can be resolved not by gross appraisals of a research structure, but by discerning evaluation of its individual components.

The presentation will be divided into two parts: an outline of the architectural structure and function of a clinical research project; and a discussion of the special ethical issues raised by different elements of different projects.

1. The Architecture of Medical Research

Of the diverse designs that can be created in the world of the arts, the plans made by an architect are the only ones that are regularly constrained by the harsh demands of reality. Since the creative activities of medical research are similarly constrained by the realistic demands of both science and people, we have used the word architecture, rather than design, to refer to the intellectual structure of projects in medical research.

1.1. The Basic Outline of the Objective

The customary starting point in an act of medical research is the investigator's statement of a question to be answered. This is the research objective. The quality of the ensuing research often depends on the clarity with which this objective is defined. It is often expressed in the form of a question: "Will B occur if X is done to A?" Examples of such questions are the following research objectives: Will headaches be relieved if treated with aspirin? Will this new vaccine prevent the development of poliomyelitis in healthy children? In non-allergic people, will antibodies be provoked by the intradermal injection of serum from patients with hay fever?

These statements each contain three distinct elements: (1) an agent or process that is the principal maneuver under investigation; (2) a direct or implied description of the baseline condition, or initial state, of the person receiving the principal maneuver; and (3) a direct or implied description of the target event to be observed after the maneuver is imposed. In the cited clinical circumstances, the principal maneuvers were, respectively, treatment with aspirin, treatment with a new vaccine, and intradermal injection of serum from patients with hay fever. The respective initial states were headache, healthy child, and non-allergic person. The respective target events were relief of headache, prevention of poliomyelitis, and development of antibodies.

The main strategy in analyzing the ethical properties of a particular research architecture is to consider the various maneuvers and procedures that are imposed upon the people being studied. The principal maneuver

is the agent or process that the investigator is most interested in studying. In the course of clinical research, however, as well as in ordinary clinical practice, many different agents or procedures, i.e., maneuvers, are also employed. Proper assessment of a medical research project requires that attention be paid to the types of maneuvers imposed; the purposes for which they are imposed; the background knowledge that sanctions their acceptability, scope, and necessity; and the way in which certain maneuvers are compared and assigned. These distinctive attributes create both the architectural and ethical challenges of clinical practice or clinical research.

1.2. Types of Maneuvers Imposed on Patients

All the procedures, processes, and agents that can be performed on patients fall into one of two categories: action maneuvers or examinative maneuvers.

1.2.1. Action Maneuvers

An action maneuver is intended to produce a persistent or temporary change in a person's condition. When an action maneuver is imposed, the baseline or initial state of its recipient is expected to change. There are two types of action maneuvers.

1.2.1.1. Interventional Maneuvers

An interventional maneuver is directly intended to produce a beneficial change in its recipient. Aspirin administered to a patient with headache is an interventional maneuver because it can give rise to a remedial improvement

in the patient's initial state, even though the improvement may only be temporary. Vaccination of healthy children against poliomyelitis is another example of an interventional maneuver. The intended change is prophylactic, in contrast to the remedial change cited in the previous example, but the initial state of the patient is modified. The maneuver produces a more beneficial subsequent state, changing the patient, from a "healthy" state of susceptibility to poliovirus infection, to a protected state of immunity.

Diagnostic breast biopsy, on the other hand, is not an interventional maneuver. Although knowledge of the results of a negative biopsy may produce benefit by relieving psychic stress, the maneuver itself (breast biopsy) does not produce the change. For a maneuver to be interventional, it must be capable of producing a beneficial effect by directly altering the state of its recipient.

1.2.1.2. Explorational Maneuvers

An explorational maneuver is performed in order to produce a change, usually transient, that is not itself expected to be beneficial. The maneuver may give rise to information that ultimately benefits the recipient, but the maneuver does not directly produce a beneficial change. A glucose tolerance test, for example, is an explorational maneuver. The overnight fast and initial glucose load create a transient physiologic change in the state of the patient. Although the change itself is not beneficial, the patient may later be helped considerably by the information that the glucose tolerance test provides.

The intradermal injection of serum from patients with hay fever into non-allergic individuals is another example of an explorational maneuver. A change of state is expected, but the new state is not expected to be an improvement. In contrast to the glucose tolerance test of the previous example, the maneuver here is not expected to yield information that will be promptly beneficial to its recipient.

1.2.2. Examinative Maneuvers

In contrast to interventional and explorational action maneuvers, examinative maneuvers are not expected to produce a significant change in the recipients. The maneuvers consist of things said or done to a person in order to observe a response as in history taking or a part of the body, as in physical examination; to obtain a sample of fluid, tissue, or excreta, as in venipuncture and urine collection; or to produce a technologic substance, as in electrocardiography or chest roentgenography. All these examples are things that are done to people, without significantly changing them. A GI series, on the other hand, is an explorational maneuver, rather than an examinative one, because the introduction of barium produces a distinct, although temporary, change in the initial state of the patient, converting the alimentary tract from being nonradio-opaque to radio-opaque.

1.3. Delineative Procedures

In contrast to the action and examinative maneuvers just discussed, which all involve the person to whom they are applied, delineative procedures are not applied to people at all. These procedures consist of the

appraisals, analyses, and transformations performed on the specimens, descriptive data, and other entities obtained from people. Both action maneuvers and examinative maneuvers, however, are invariably accompanied by delineative procedures. For example, the value of a blood hematocrit is obtained by means of a delineative procedure performed on blood obtained from a person by means of venipuncture, an examinative maneuver. Similarly the determination of blood glucose levels in a glucose tolerance test, the microscopic analysis of a surgically removed lung, and the intellectual appraisal of a history and physical examination to arrive at a diagnostic impression, are all delineative procedures based on the prior application, respectively, of explorational, interventional, and examinative maneuvers.

Since the performance of a delineative procedure entails no risk or discomfort to the patient, such procedures themselves create few ethical problems with respect to either the subjects of human research or the patients in ordinary clinical practice, who provide the raw material exposed to the delineative procedures. The ethical aspects of delineative procedures arise from the way in which the results of those procedures are used. Results that can be misused or misinterpreted in a way that might harm a patient create ethical concerns, but the procedures themselves are ethically "neutral."

1.4. Purposes of Maneuvers

The various types of action and examinative maneuvers described in section 1.2. can be applied for three basic purposes: explicatory, clinical, and preclinical.

1.4.1. Explicatory Maneuvers

A maneuver used for an explicatory purpose is intended to illuminate or explain a biological phenomenon. Such maneuvers are employed in physiologic, biochemical, pharmacodynamic, or other studies in order to help explain some feature of the patient's condition, or a mechanism of the maneuver itself, or both. For example, when a patient with diabetes mellitus receives an infusion of sulfate to study its effect on the renal excretion of potassium, the sulfate infusion is an explorational maneuver employed for an explicatory purpose. The immediate goal of the maneuver is not to improve health, not to ameliorate a manifestation of diabetes, and not to prevent a future diabetic vascular complication, but rather to help explain mechanisms of diabetic renal function. Furthermore, the information derived from the imposition of the maneuver is not expected to yield any immediate benefit for the patient.

1.4.2. Clinical Maneuvers

Maneuvers performed for a clinical purpose are intended to provide direct or indirect benefits for their recipients.

1.4.2.1. Diagnostic Maneuvers

The aim of a maneuver performed for a diagnostic purpose is to produce information that will be useful in the clinical care of the person who receives the maneuver. The diagnostic process may require the imposition of different types of maneuvers, such as the examinative maneuver of a blood culture, the explorational maneuver of a BSP test, or the interventional

maneuver of antibiotic therapy in a patient with a fever of unknown origin.

1.4.2.2. Therapeutic Maneuvers

Maneuvers employed for therapeutic purposes are interventional. They are performed to produce a beneficial change in their recipients. The goal may be prophylactic, to prevent some adverse future event; or remedial, to alter or remove some existing undesirable manifestation. The administration of a vaccine anticipated to prevent smallpox is an example of a prophylactic interventional maneuver, as is the procedure of retinal photocoagulation to prevent blindness in appropriate diabetic patients. Appendectomy for appendicitis and aspirin for headache are examples of remedial interventions.

1.4.3. Preclinical Maneuvers

Maneuvers undertaken for preclinical purposes are explorational or examinative. Although not expected to benefit their recipients, they are expected to lead directly to new interventional or explorational maneuvers having clinical value. Like explicatory maneuvers, preclinical maneuvers are intended to yield information useful to the investigator but not immediately useful or helpful to the recipient of the maneuver. Unlike other explicatory maneuvers, however, preclinical maneuvers are expected to serve as a direct prelude to the development of diagnostic or therapeutic procedures.

For example, in Phase I studies of new pharmaceutical agents, healthy volunteers or patients receive the drug for the purpose of determining pharmacokinetics, dose-response curves, acute toxicity, bioavailability, or pre-

liminary evidence of therapeutic safety. The purpose is preclinical because of the hope that the successful completion of the Phase I studies will yield the information needed to allow the new agent to advance to therapeutic applications. Similarly, the preliminary evaluation of a proposed new serologic test for gonorrhoea will not directly benefit those patients who undergo the examinative maneuvers (venipuncture) that the study entails, but the purpose of those maneuvers is preclinical because of the expected demonstration of diagnostic usefulness for the new test.

1.5. Multi-purpose Maneuvers

Most maneuvers are employed for a distinct single purpose. The aspirin is given to relieve a headache or blood is drawn to determine a diabetic patient's blood glucose, the sole purpose of the maneuver is usually clinical. Occasionally, however, the same maneuver is used for multiple purposes. A maneuver employed for a primary clinical goal may also interest an investigator for explicatory purposes. Thus, the aspirin that a patient received clinically for a headache may be simultaneously viewed as an explicatory maneuver that, with suitable examinative procedures, can help explain the action of aspirin on platelets. When a blood sample is drawn as an examinative maneuver for the clinical purpose of determining glucose in a diabetic patient, the additional determination of blood glucagon in the sample can make the examinative maneuver also serve an explicatory purpose.

For these two examples, the purpose of the main maneuvers is clinical from the point of view of the patient and his personal physician, but expli-

catory from the point of view of an investigator. These different points of view can enable a single maneuver to have multiple purposes. The ethical justification for the imposition of a maneuver should always be first considered according to the maneuver's primary purpose, as viewed by the patient or his personal physician. Thus, in the cited examples, the primary purpose of both maneuvers is clinical.

In medical research activities, an investigator may sometimes add an explicatory purpose onto a maneuver whose primary aim is clinical. For example, an investigator who wishes to study the behavior of macrophages in human lung tissue might arrange to receive specimens of such tissue from patients undergoing pneumonectomy as clinical treatment for lung cancer. This sort of "piggyback" research can often circumvent the ethical difficulties of using a maneuver whose primary purpose is explicatory. The investigator, in this example, avoids the ethical problems involved in asking volunteers to undergo open lung biopsy.

1.6. The Sanction of Maneuvers

A maneuver can be regarded as sanctioned (or nonsanctioned) according to its general acceptance, scope, and necessity.

1.6.1. General Acceptance

A maneuver that is part of the ordinary, generally accepted procedures of the medical armamentarium can be called an established maneuver. Among such maneuvers are pharmaceutical agents, such as aspirin and digitalis; surgical procedures, such as appendectomy; explorational maneuvers, such as

coronary angiography; and examinative maneuvers, such as venipuncture and chest roentgenography.

Maneuvers become established in various ways. Some agents, such as birth control pills, become generally accepted as a result of scientific studies demonstrating their efficacy and relative safety. Other agents, such as digitalis and aspirin, became established as a result of traditional use in medical practice. A third mechanism of acceptance is academic enthusiasm, which can often lead to widespread usage of new procedures and therapies that have received neither rigorous scientific study nor traditional usage. The academic approbation is not always vindicated. A notorious example of mistaken academic enthusiasm was the widespread use, 25 years ago, of high-dosage oxygen for premature babies. Although rapidly accepted, this new treatment was later shown to have little or no therapeutic benefit, while often causing blindness due to retrolental fibroplasia. The enthusiastic adoption of such maneuvers can often be traced back to a mistaken physiologic rationale, in which the therapy "makes sense" and follows logically from accepted (but erroneous) biological theories of the day.

A non-established maneuver is a procedure or agent that is not generally accepted in ordinary clinical practice. The use of a hypothetical new drug such as "curitol," proposed as a treatment for baldness, would be a non-established maneuver because the actual merits and dangers of "curitol" are unknown. The use of thalidomide, on the other hand is now non-established because of its known toxicity. Thus, maneuvers may be non-established be-

cause their consequences are unknown in ordinary clinical practice or because they are known and not accepted.

1.6.2. Scope of an Action Maneuver

The scope of an action maneuver is standard when it is established and its primary purpose is accepted in ordinary clinical practice. Aspirin used for relief of headache and penicillin for eradication of streptococcal infection are examples of maneuvers used in a standard way. In both these examples, the initial condition and subsequent target for which the maneuver was employed correspond to the circumstances in which the maneuver is employed in ordinary clinical practice.

An action maneuver is used for a nonstandard scope when an established maneuver is employed for a condition or aimed at a target event that is different from what would occur in ordinary clinical practice. Aspirin used to prevent strokes in patients with transient ischemic attacks, and digitalis used to treat patients with obesity, are examples of established maneuvers used in nonstandard ways.

1.6.3. Necessity of Examinative and Explorational Maneuvers

Most of the examinative and explorational maneuvers employed in ordinary clinical practice are regarded as necessary for the care of the patient. Examinative and explorational maneuvers are warranted if their use is justified by clinical necessity. For example, electrocardiographic monitoring during acute myocardial infarction is a warranted examinative maneuver because of its accepted, necessary role in the proper clinical management of such patients.

In the course of medical research, and occasionally in ordinary practice (especially at academic centers), maneuvers are imposed to obtain data that may be useful for research or teaching purposes, although not necessary for the clinical care of the patient. Such maneuvers can be called non-essential. As an example, suppose an investigator, suspecting that aspirin affects the metabolism of alkaline phosphatase, arranges to measure the serum alkaline phosphatase levels before and after the clinical administration of aspirin to patients with ordinary headaches. The aspirin treatment would be an act of ordinary clinical therapy, representing the standard use of an established maneuver. The acquisition of data about alkaline phosphatase, however, requires the performance of venipuncture, which would here be a non-essential examinative maneuver, performed to help explicate the mechanism of action of aspirin.

1.7. The Arrangement of Maneuvers

Medical research often requires maneuvers to be administered in a way that allows their effects to be compared. An important part of the architecture of medical research is devoted to the arrangements for such comparisons.

1.7.1. Comparative Maneuvers

Although the principal maneuver is the agent or process in which an investigator is most interested, the events that follow its imposition are not always caused by that maneuver. Consequently, investigators must beware of the erroneous conclusions produced by post hoc ergo propter hoc reasoning if the principal maneuver is used alone. The main method of avoiding such errors

is to study a comparative maneuver, or "control." By observing the results that occur when the comparative maneuver is applied to the same initial state in a different person (or in the same person, when feasible), the investigator can more judiciously evaluate the accomplishments of the principal maneuver.

The choice of the agent or procedure employed as a comparative maneuver depends upon the research objective. If the objective deals with absolute efficacy -- what does the principal maneuver accomplish? -- the comparative maneuver is usually an inert entity that mimics the principal maneuver but that lacks its main active ingredient. The comparative maneuver may thus be a placebo, an injection of saline, a lotion composed only of the vehicle in which an active steroid was dissolved, a sham surgical operation, or no treatment at all.

If the research objective deals with relative efficacy -- does the principal maneuver work as well as some other maneuver? -- the comparative maneuver consists of an agent or procedure whose action is to be contrasted. In this way, a new treatment may be compared against an established old treatment, or two old established treatments may be compared to see which is better.

The comparative maneuver may sometimes be applied sequentially to the same persons who receive the principal maneuver. Such situations are called cross-over studies. They are common in explicatory circumstances, where the transient effect of the maneuvers is often brief enough to allow the same person to receive all of the various maneuvers under comparison. Cross-over studies can also be conducted for therapeutic purposes, but are applicable

only for a limited number of maneuvers and clinical conditions. In a parallel study, which is used occasionally in explicatory and commonly in therapeutic activities, one group of persons receives the principal maneuver and another group, the comparative maneuver. Regardless of whether a parallel or cross-over arrangement is used, the planned therapeutic comparison of a principal vs. another maneuver is called a clinical trial.

1.7.2. Planned and Unplanned Comparisons

In ordinary clinical practice, different therapeutic decisions are made in an ad hoc manner. When these decisions have produced substantial experience with different maneuvers, an investigator may collect the data and perform a research survey to contrast the outcomes of the several maneuvers. For example, many of the studies of the therapeutic usefulness of anticoagulants in myocardial infarction or of diverse treatments for cancer were performed by reviewing the records and comparing the outcomes of patients in whom different ad hoc therapeutic decisions had been made. The results of the maneuvers were compared, but a deliberate comparison had not been planned when the maneuvers were imposed.

In a research experiment on the other hand, the maneuvers under comparison are assigned according to a deliberate research design. In most modern clinical trials, the allocation of either the principal maneuver or the comparative maneuver to a particular patient (or the choice of the sequence of maneuvers in a cross-over study) is accomplished by means of randomization. For example, if propoxyphene (Darvon^(R)) is being compared with aspirin for relief of headache in a clinical trial, randomization would ensure that each

patient has an equal chance of receiving either agent, by eliminating the judgment, whims, and prejudices of the investigator when the assignment is made.

1.7.3. Method of Observation

Although randomized allocation of maneuvers has been a major advance to improve scientific validity in clinical research methods, another major scientific improvement has been the use of techniques that help eliminate bias when the effects of the maneuvers are observed. In the single-blind technique, patients are kept unaware of the particular maneuver they are receiving. In the double-blind technique, the exact identity of the imposed maneuver is unknown to both the patient who receives it and the investigator who observes and assesses the subsequent effects. Occasionally, as in anticoagulant therapy, the regulation of dosage requires a knowledge of the treatment and of certain pharmacologic effects. In such circumstances, a double observer technique may be employed. One physician, aware of treatment, regulates the dosage. The other observer, kept "blind," notes the other effects. No matter how the double-blind technique is arranged, adequate safeguards must be established to allow the physician to identify the maneuver if an untoward reaction should occur.

1.8. Research vs. Ordinary Clinical Practice

The foregoing discussion has shown the similarity of many activities that occur both in research and in ordinary clinical practice. By considering the cited architecture for types, purposes, sanction, and arrangement of maneuvers,

the distinctions between research and ordinary clinical practice come into sharper focus.

1.8.1. Characteristics of Ordinary Clinical Practice

Although all types of maneuvers -- interventional, exploratory and examinative -- can be used in ordinary clinical practice, the primary purpose of the maneuvers is always clinical. Action maneuvers are generally sanctioned as established and standard; examinational and exploratory maneuvers are generally sanctioned as established and warranted. Furthermore, in ordinary clinical practice no plans are developed for deliberate testing of comparative maneuvers.

1.8.2. Characteristics of Research

As in ordinary clinical practice, all types of maneuvers can be used in medical research. In contrast, certain other features are found almost exclusively in research activities.

1.8.2.1. Explication

Maneuvers employed primarily for explicatory purposes are not a feature of ordinary clinical practice. When a maneuver's primary purpose is explicatory, the activity is research, not practice; and many explorational maneuvers are regularly used with primary explicatory purposes that are often quite far removed from the goals of ordinary clinical practice.

1.8.2.2. Preclinical Maneuvers

Preclinical maneuvers also occur exclusively in research activities.

Because such maneuvers are direct preludes to clinical maneuvers, the situations in which they are used are generally closer to ordinary clinical practice than those of explicatory maneuvers.

1.8.2.3. Nonstandard Action Maneuvers

Established action maneuvers, when used for a nonstandard scope, are generally part of a research activity, and are usually tested with a comparative maneuver. Occasionally, however, established maneuvers are used in ordinary practice in ways which can not yet be called standard, but are not part of a specific research design. An example of such a situation is a physician's prescription of aspirin to prevent recurrent transient ischemic attacks.

1.8.2.4. Non-essential Maneuvers

Although frequently present in research activities, non-essential examinative and explorational maneuvers are occasionally used in ordinary clinical practice, particularly at academic centers, for pedagogical purposes. The number of non-essential maneuvers can often be minimized in research by using warranted maneuvers for multiple purposes, as discussed in section 1.5.

1.8.2.5. Acts of Comparison

In the circumstances just cited, an act of research could be identified by the way a particular single maneuver was employed. Other clinical activities become identified as acts of research not via the function of a single maneuver, but via a comparison of two or more maneuvers. A pre-planned comparison is often, in fact, the distinction that separates many acts of medical

research from those of ordinary clinical practice. The introduction of a pre-planned comparison can often transform into research something that would otherwise be regarded as ordinary medical care. For example, a clinical trial of medical vs. surgical therapy for stable angina pectoris is a comparison of two therapeutic interventions that are both ordinarily considered as established, customary treatments. If allocated to individual patients by ad hoc judgments, the treatments are acts of ordinary care. If allocated by a pre-planned randomization, the same treatments are part of research. This type of medical research, comparing one standard therapeutic maneuver with another, often quite closely resembles ordinary clinical practice and presents a minimum of inherent ethical difficulty. Comparisons that involve explicatory or preclinical maneuvers, or that test clinical maneuvers for nonstandard or non-established scopes, are further removed from ordinary clinical practice and present greater ethical challenges.

2. Ethical Issues in Research

Since the main ethical difficulties in medical research arise from what is done to the patient, why it is done, and whether it receives the patient's consent, the research activities performed on patients require careful analysis. The taxonomy that has just been described for maneuvers and other aspects of research architecture can be a powerful tool in that analysis by providing a clear "dissection" of the structure and purpose of diverse medical activities. In this section we shall use that new taxonomy in brief discussions of several types of ethical issues.

2.1. Issues in the Purpose of Maneuvers and Procedures

The primary purpose for which a maneuver is employed has important ethical implications. For example, giving a toxic agent, such as nitrogen mustard, to a healthy volunteer for explicatory purposes might be regarded as patently unethical (even with informed consent), yet the same agent could be readily justified if given for clinical purposes to a patient with Hodgkin's disease for clinical purposes.

2.1.1. Clinical Purposes

Of the diverse maneuvers used in research, the ones that are administered for clinical purposes have the strongest resemblance to the activities of ordinary medical practice. Thus, therapeutic maneuvers that are established and used in a standard way should create no greater ethical difficulty in research than they do in ordinary practice. Nonstandard and non-established maneuvers present progressively greater difficulties because their potential risks and benefits are progressively less well known. Persons exposed to nonstandard or non-established clinical therapeutic maneuvers, therefore, should be especially well informed of the possible consequences of their exposure.

Similarly, when a diagnostic maneuver that is used in research is also warranted, its performance is ethically justifiable in the same way as in ordinary clinical practice. Because most diagnostic maneuvers present little potential risk or discomfort, the ethical difficulty is usually small, even if the maneuver is non-essential. On the other hand, maneuvers that entail

significant risk, such as cardiac angiography, may present thorny problems if they are non-essential.

When clinical circumstances warrant their use, non-established diagnostic maneuvers, such as transvenous myocardial biopsy, can be regarded in the same way as other non-established clinical maneuvers. If their use is not expected to provide information of importance to the patient, non-established diagnostic maneuvers are not really diagnostic at all, and should be regarded as having an explicatory purpose.

2.1.2. Explicatory Purposes

When the primary purpose of a maneuver is explicatory, it offers no benefit to its recipients. Special attention must therefore be paid to the harmful potential of such a maneuver. If the maneuver is established, such as using caffeine to stimulate gastric acid secretion, the risks may be known and the ethical import of the explicatory activity is easy to assess. Difficulties arise for maneuvers that are non-established. When the potential risks can only be guessed, the investigator should be expected to amass as much preliminary information as possible, including the results of animal studies, about toxicity. Recipients of explicatory maneuvers should always be fully informed in advance about possible untoward reactions.

2.1.3. Preclinical Purposes

Preclinical maneuvers ethically resemble explicatory maneuvers in that the recipients are not expected to benefit. Since preclinical maneuvers, however, are more likely than explicatory maneuvers to lead to immediate

clinical rewards, preclinical maneuvers can be regarded with slightly more benignity. Nevertheless, their possible toxicities should be fully investigated and disclosed in advance to all research subjects.

2.1.4. Delineative Procedures

Delineative procedures, not being performed on patients, can themselves neither harm nor benefit patients. The only ethical safeguards needed for delineative procedures arise from the use of the results. If a result can affect a patient's clinical management or some other significant aspect of life (such as eligibility for life insurance), careful precautions must be taken to ensure that the procedure is performed and interpreted correctly, that the results are kept confidential, and that the patient's consent is obtained for any disclosure. On the other hand, if the results of a delineative procedure will not affect the patient in any way, the performance of that procedure does not create an ethical issue for that patient. To obtain the patient's consent for performing the procedure is unnecessary. For example, a patient's consent would not be required for a research pathologist to examine macrophages taken from a lung that was removed by a clinically justified pneumonectomy.

2.2. Issues in the Necessity for Research

By inquiring about the purposes, sanctions, and comparison of maneuvers, we can determine whether they are being used for acts of research. The next step is to inquire about the reason or necessity for the research itself.

2.2.1. The Need for Explicatory Maneuvers

Today's achievements in medical science largely depend on yesterday's advances in the understanding of human biology. Our current ability to transfuse blood, transplant kidneys, prevent poliomyelitis, alter cardiac arrhythmias, and replace bones is the ultimate clinical consequence of progress for which the groundwork was laid by research using explicatory maneuvers. Since no animal model can totally duplicate human biological phenomena, explicatory maneuvers must often be tested in people to increase the basic fund of medical knowledge that may eventually benefit all mankind.

With imaginative perception, however, investigators can sometimes take advantage, for explicatory purposes, of maneuvers administered for other reasons. Such research can be performed by grasping the opportunity to observe the results of maneuvers imposed by nature, by doctors in the course of ordinary clinical care, or by patients themselves. For example, knowledge of the pharmacokinetics of certain drugs has been greatly augmented by the study of patients who receive these drugs in ordinary therapy or who deliberately take overdoses. The atomic bombing of Hiroshima and Nagasaki allowed investigators to study the effects of intensive radiation exposure in humans. The natural occurrence of certain inherited enzyme deficiencies in people has led to important clarifications in understanding human biochemical pathways. In all of these examples, an investigator who might have been ethically unwilling or unable to ask volunteers to receive the studied maneuvers could avoid the otherwise thorny ethical problems of such research.

2.2.2. The Need for Therapeutic Maneuvers

Therapeutic maneuvers are evaluated in medical research to establish whether or not a treatment is safe and effective for a particular condition. Such research is necessary because therapeutic efficacy and safety in people cannot be predicted with certainty despite elaborate scientific theories and extensive animal investigations. Many "established" therapeutic maneuvers -- such as the bloodletting and purging of a century ago and the excessive oxygenation of premature babies in the most recent past -- ultimately turn out to be ineffective or tragically unsafe. The testing of new treatments and comparative testing of old treatments is needed to protect all patients from the harm that might come if a relatively small proportion of patients did not participate in research on therapeutic maneuvers.

2.2.2.1. Transmutability of Efficacy

The efficacy of a therapeutic agent refers to the ability of that agent to produce a particular result for a particular condition. In the research that establishes the efficacy of an agent, its scope is determined by the clinical conditions and the associated effects or target events for which it is given. The research can establish the agent's efficacy only for the scope that has been investigated. Suppose, for example, that relief of pain is chosen as the only target event under examination in a clinical trial of steroids vs. placebo in treatment of peptic ulcer disease. Although the steroids will probably seem quite effective for relief of pain, they will not have been shown effective for healing the ulcer -- a target that was not

tested. In fact, steroid treatment in patients with peptic ulcer disease may regularly relieve pain while also leading to perforation, sepsis, and death.

The issue of transmutable efficacy -- deciding whether an agent that is demonstrably effectively for one scope can be safely regarded as effective for another -- sometimes raises interesting problems in the evaluation of ethics. When Beecher⁽¹⁾ in 1966 condemned as unethical an interventional experiment in which penicillin was withheld in a group of patients with streptococcal pharyngitis, he stated "it is known that rheumatic fever can usually be prevented by adequate treatment of streptococcal respiratory infections by the parenteral administration of penicillin." When the particular study Beecher cited was performed ten years earlier, parenteral penicillin had been established as an agent that could eradicate streptococcal pharyngitis, but a further scope had not been demonstrated. Doctors did not know whether treatment of streptococcal infections with penicillin would produce a different effect: prevention of rheumatic fever. Ironically, the reason that the antirheumatic prophylactic efficacy of penicillin was so well known in 1966 was mainly because of the results found in the very study that Beecher attacked.

If therapeutic agents had an unbounded scope, so that one form of efficacy could readily be transmuted into another without any uncertainties or needs for additional scientific evidence, some of the prime therapeutic dilemmas of our era could be instantly eliminated. There would be no need to ask pharmaceutical companies to show that an anorexigenic agent leads to weight loss in patients with obesity. The demonstration of anorexic action

alone would suffice. There would be no need to compare the results of medical therapy to see whether a vascular graft, which obviously provides an anatomic remedy for coronary artery obstruction, also reduces angina, prevents cardiac deterioration, and prolongs life. Because efficacy, however, cannot be transmuted, its attempted conversion will continue to create major uncertainties. The clinical investigations needed to answer all questions would seem ethically justified by the uncertainties.

2.2.2.2. Investigations to Acquire "Soft Data"

The choice of the target events studied in the investigation of therapeutic maneuvers obviously has major importance. Unfortunately, the current "scientific" obeisance to objective "hard data" has made most modern evaluations of therapy depend on a choice of target events that consist of easily measured reliable effects, such as death, size of X-ray shadows, and electrocardiographic changes. The "soft data" that describe the uniquely human clinical phenomena of sick people are usually deliberately ignored as being too subjective to receive "scientific" attention. Applying this scientific standard, investigators usually evaluate white blood count but not pain; size of tumor but not ability to work; change in serum enzymes but not change in family relations; quantity of survival but not quality of life.

Consequently, when a treatment is determined to be effective and safe, little or no consideration may have been given to its effect on the personal or symptomatic aspects of human illness. As a result, well-intentioned doctors and patients may be misled into thinking that a therapy shown to be scientifically effective is actually the best therapy. Failure to consider

"soft data" often produces the iotrogenic misery of toxic drugs, surgical mutilations, and calamitous expense.

Because a therapeutic maneuver may be certified as safe and effective after scientific research that ignored important "soft data," further research may often be necessary to fill in the gaps about human suffering or gratifications. A valuable ethical constituent of therapeutic effectiveness may be the inclusion of important "soft data." Reliance on "hard data" alone may often have all the advantages of scientific objectivity, but almost none of the humanistic or scientific merits of a concern with the total spectrum of a treatment's impact. Research that leads to the widespread use and acceptance of a therapeutic maneuver might sometimes be considered ethically remiss if crucial "soft data" were omitted from the evaluation.

2.2.2.3. The Value of a "Negative Result"

When a clinical trial is successful, the results can be directly and immediately used in clinical practice. If treatment A is shown to be superior to treatment B, or vice versa, all patients can benefit as soon as the new knowledge is disseminated. Furthermore, a patient who received the "inferior" treatment during the trial might even be able to benefit, immediately after the trial, by transfer to the treatment that his participation helped establish as superior.

Although an investigator beginning a clinical trial expects its results to indicate a significant difference between the agents compared, even a "negative result," i.e., one that indicates no difference, can be valuable.

A clinical trial showing that a particular agent is therapeutically equivalent to a placebo prevents that agent from becoming accepted, thus providing a potentially valuable service to patients. For example, suppose several preliminary reports reveal that an expensive new (but actually hazardous and worthless) drug "curitol" cures the common cold. Without a clinical trial to demonstrate the lack of efficacy, millions of people might otherwise have been subjected to this costly and slightly risky agent.

A clinical trial showing that a new non-established agent is therapeutically equivalent to an old established agent can be valuable in many ways. The new agent may prove quite useful in patients who have had adverse reactions to the established therapy. Differences in cost or convenience might make the new agent preferable in certain patients. Furthermore, the new agent might be found to be useful in patients for whom the established therapy is ineffective.

Thus, a clinical trial can be valuable even when the outcome is a "negative result." If the research is designed properly, patients who participate in it have a considerable chance of helping themselves and other similar patients no matter what the outcome.

2.3. Communication with the Patient

A patient who participates in medical research has a unique relationship with the investigator, depending in large part on the primary purpose of the principal maneuver.

2.3.1. Clinical Maneuvers

A patient who receives a clinical maneuver in medical research is primarily motivated by the desire for good medical care and by the chance of receiving a possibly superior treatment. Such a patient regards therapeutic promise as the main thrust of the research and perceives the imposition of the principal maneuver (or comparative maneuver) as an act of treatment given by someone who assumes the responsibility of being the doctor. This type of patient wants the investigator to be more a good doctor than a good scientist. Although aware of the experimental nature of the research activity, the patient usually expects (and deserves) a traditional doctor-patient therapeutic relationship with the physician who renders the clinical care.

In ordinary clinical practice, the exchange of information between doctor and patient is a crucial part of the therapeutic relationship. The doctor's empathy, authority, and power of suggestion not only influence the way the patient feels, but often influence the actual course of disease. The doctor must therefore do more than passively convey information. He must carefully choose what he says and how he says it. Should he tell a patient immediately that he suspects cancer, or wait until the definitive diagnosis is made? Most doctors would wait, and most patients would want them to wait. When therapy is proposed in ordinary practice, most doctors do not inform patients of all possible risks and side effects. The therapeutic relationship presupposes that to a certain extent the physician will exercise his judgment in the best interests of the patient. To do otherwise would violate the spirit and value of the doctor-patient relationship.

An investigator who imposes a maneuver for clinical purposes may sometimes be placed in a difficult position. For the therapeutic benefit of certain patients, the investigator, as a doctor, may want to withhold information that could have adverse effects on the patient's morale or psychic status. Withholding information, however, leaves the investigator, as a scientist, open to the charge that unappealing details were deliberately withheld in order to ensure the patient's participation in the research.

Irving Ladimer⁽¹⁰⁾ has proposed that "explanation may be limited if it can be demonstrated that risk or harm to the patient by such explanation is proportionally greater than the risk involved in the proposed activity." In contrary opinions, the belief is that willful withholding of information in medical research -- as well as in ordinary practice -- is never ethically justifiable.

It seems reasonable to suggest that patients who are to receive non-established maneuvers (as described earlier) be fully informed about the potential risks, discomforts, and inconveniences. The recipient of a non-established maneuver is to some extent in uncharted waters. He deserves to know the risks of the voyage before he agrees to embark on it. If the investigator believes that it is not in the best interests of the patient to know these risks, then it is probably not in the best interests of the patient to participate in the study. Although the investigator may believe that the risks are small, he cannot know that the risks are small if the maneuver in question is non-established. Consequently, a patient asked to take a potentially serious risk should be made aware of the existence of that risk.

On the other hand, in certain circumstances an investigator may be justified in withholding information from a patient about to receive an established maneuver. For such maneuvers, the risks to which a patient will be exposed have usually been ascertained. The investigator can have some confidence in his belief that a particular risk is small. Furthermore, for either standard or warranted maneuvers, the risks incurred are analogous to the risks that would be incurred in ordinary practice. As in ordinary clinical practice, the patient in a medical research project, who receives a maneuver for clinical purposes, must rely to a large extent on the good intentions and clinical competence of his doctor. Although communication between doctor and patient should be as full and complete as possible, the investigator will sometimes need to exercise restraint and judgment in the best interests of the patient. As Campbell⁽²⁾ has pointed out: "The only real protection for the individual lies in the scrupulousness, conscience, and personal integrity of the investigator."

2.3.2. Explicatory Maneuvers

In imposing maneuvers for explicatory purposes, an investigator is not engaging in therapy and may not need to enter into a therapeutic relationship with the patients who are his subjects. An explicatory experiment can often be conducted while the patient is under the basic care of some other doctor. It is important, however, that the patient not confuse what is done for his benefit with what is done for the sake of research. Although such confusion is less likely to occur if the patient's basic medical care is supervised by someone else, the investigator sometimes functions both as researcher and as personal doctor.

A patient may thus be asked by his personal doctor to receive an explicatory maneuver as part of a research activity in which that same doctor is the investigator. This dual activity by the same physician may easily mislead the patient into believing that he will in some way benefit from the research. For such situations, it is especially important that the explicatory nature of the maneuver be carefully explained to its potential recipients.

2.4. Issues in the Design of Research

All the ethical issues just cited arise from the viewpoint of a person exposed to a research maneuver. A different set of ethical issues can be approached from the viewpoint of the investigator, the medical profession, and the future patients who will be affected by the results.

2.4.1. The Research Objective

Research that puts human subjects at risk should be worthwhile doing. Expertly planned, rigorously executed, scientifically impeccable research can sometimes be applied to an objective so nugatory or poorly conceived as to be almost worthless. A person should not be asked to participate as a subject in an experiment that may risk his well-being if the experiment will have little value for science or society. A major responsibility of the investigator and of the ethical review committee is to ensure that people are not devalued by being asked to participate in trivial or bad research.

Before a research proposal reaches the stage of review for the ethical issues it raises, the protocol should first receive thorough, critical appraisal of its scientific goals, plans, feasibility, and significance. To allow such appraisal, the statement of the research objective must provide enough information to enable a scientifically sophisticated reviewer to evaluate the proposed investigation. A confusing or unclear description of the research objective will raise doubt about the scientific merit of the proposal, while also obscuring its ethical merits.

2.4.2. The Validity of the Overall Design

The details of a research proposal translate the research objective into a concrete plan of action. If the plan of action is poorly designed, the objective will be met inconclusively or not at all. Although questions of validity in research design are traditionally regarded as purely scientific problems, scientific validity becomes an ethical issue when people are asked to participate in an experiment. Poorly designed human research is unfit for human subjects.

A research design that leads to specious conclusions may also be unethical because of the possible consequences of those conclusions. For example, when an inadequately performed retrospective case-control study produces false claims of toxicity for a well established treatment or for an act of daily life (such as coffee drinking or breast feeding), the needless fear, distress and other adverse psychic effects of the false report must receive appropriate ethical consideration. Similarly, if a clinical trial mistakenly purports superiority for a new therapy, future patients may be subjected to

the possible harm of an ineffective new agent, while simultaneously being deprived of whatever benefits the old therapy might produce.

Furthermore, specious conclusions from badly designed human experiments can be extremely difficult to countermand. Despite persistent doubts about investigative architecture and methods, the research may not be repeatable because of its technical difficulties, its logistic problems, or the ethical qualms that were created by the original, possibly erroneous report. When the results of a large-scale human experiment are seriously questioned, as in the controversy occasioned by the University Group Diabetes Program (UGDP) study,⁽⁵⁾ ⁽¹²⁾ investigators and practitioners may both be left in an ethical quandry. Should practitioners abandon a heretofore established therapeutic agent because of results found in research whose scientific design is unacceptable to many thoughtful clinicians and epidemiologists? Should a new group of investigators attempt to repeat the study, correcting its methodologic flaws, but exposing new groups of patients to a therapeutic agent that may be harmful (if the first study was correct)? As Kabat⁽⁹⁾ has pointed out, "Is it ethical to do a study on human subjects with a design such that one may come up with the wrong answer or no answer?"

Because of many currently unresolved problems in the design of clinical research, the value and reliability of a particular investigation cannot always be assessed or predicted in advance. A simple research design may seem adequate to meet a modest objective, but final results do not always conform to initial expectations. Nevertheless, the data often tempt an investigator to infer unwarranted but tantalizing conclusions. Such conclu-

sions sometimes achieve a high degree of acceptability, despite the absence of the necessary additional studies. The increasing acceptance of such conclusions decreases the likelihood that a valid scientific study will later be performed. Investigators who doubt the veracity of accepted "facts" or "conventional wisdom" may not be motivated enough to overcome the technical and ethical obstacles of repeating a human experiment.

2.4.3. Inaugural Randomization vs. Historical Controls

The risk of premature acceptability is especially high for new therapeutic maneuvers, because clinicians seeking better methods of treatment are often tempted by laudatory reports of new therapies whose value has not been conclusively proved. By the time an experiment is conducted to provide conclusive proof, the treatment may be so thoroughly accepted that the comparative testing of a "control" group is regarded as unethical. This problem has led some commentators, particularly Chalmers,⁽³⁾ to advocate that new therapeutic agents be inaugurated in humans only in the setting of a randomized clinical trial. Chalmers has stated that uncontrolled early "pilot studies" -- in which all patients receive the new treatment, with none getting a concurrent comparative maneuver -- are potentially unethical because of the risk of premature acceptability. According to Shaw and Chalmers,⁽¹¹⁾ "Years may elapse before members of the medical profession slowly realize that the therapy is not as good as claimed. Meanwhile, hundreds of thousands of patients have been poorly treated. The opposite also surely occurs -- promising therapies are discarded because they were not given a fair trial."

The advocates of inaugural randomization would disallow the "pilot" research that may evoke unwarranted conclusions. By compelling the initial use of all new therapeutic agents to occur in the setting of a randomized clinical trial, Chalmers believes that valid conclusions are more likely to be obtained, thereby serving both science and ethics.

The opposing viewpoint, for which Freireich⁽⁸⁾ has been a leading proponent, is that ethical and technical difficulties would prevent investigators from assembling the relatively large numbers of patients needed to conduct randomized clinical trials for each of the large number of new therapeutic agents that are constantly being developed. The alternative proposal is to perform small pilot studies initially and to compare the results found for the new therapeutic agents against the data of "historical controls" with patients treated in the past with an old therapy.

This pilot-study-vs.-historical-control approach would eliminate the ethical dilemma of an investigator who sincerely believes in the superiority of an untried new therapy and who therefore feels reluctant to deny it to eligible patients. On the other hand, in the absence of better methods for demonstrating that the "historical controls" and the pilot-treated patients were prognostically similar before treatment began,⁽⁶⁾ the comparison of the non-randomized therapies may produce distorted results because of unrecognized bias in the choice of patients subject to the compared treatments.

The controversy, which is still unresolved, merits attention here because it illustrates how problems of research architecture and scientific validity become intertwined with issues in ethics.

Since inaugural randomization cannot be feasible because it cannot be conducted ubiquitously, and since current taxonomic classifications are inadequate to create valid comparisons for "historical controls," neither proposal alone seems likely to solve the existing scientific and ethical dilemmas. A possible solution is to create improved systems of clinical taxonomy, thereby allowing historical controls to be used for many minor studies, while reserving randomized trials for major therapeutic uncertainties.

3. Conclusion

The ethics of medical research depend upon the architectural components of the research. These components have been described in a system of classification that can greatly aid the intellectual "dissection" of research according to the types, purposes, sanction, and comparison of medical maneuvers and procedures. The distinctions noted in these different entities can help clarify the focus of issues in both the scientific and ethical evaluation of clinical investigation.

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10

HOW TO IDENTIFY ETHICAL PRINCIPLES

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An Essay

prepared for the National Commission for
the Protection of Human Subjects of Biomedical
and Behavioral Research on the subject of
How to Identify Ethical Principles: that is
1) How to recognize what arguments and
considerations, rules of actions, objections,
etc. can properly be acknowledged as "ethical",
and 2) How they are to be distinguished from
and related to, other kinds of arguments and
considerations (e.g. legal or technical,
esthetic or political) that bear on the
acceptability or inadmissability of human
actions.

What do we and what ought we to mean by 'ethical'? If we go to the standard dictionary definitions we shall find in modern English at least three distinct ways of using the word. First of all and most importantly it is often simply a synonym for 'moral.' Secondly it is sometimes restricted so that it is applied to moral utterances only when they are viewed as expressions of principles or bodies of moral theory. So 'ethics' is the name of systematic, philosophical enquiry into the nature of morality. Thirdly, 'ethical' and 'unethical' are sometimes applied directly to conduct. Usually although not always this third type of use has reference to some special set of standards, more especially professional standards.

In this essay I shall use the word 'moral' in place of 'ethical' for the first type of use; and I shall reserve 'ethical' itself for the third type of case. This is the way of using these words that seems to accord most nearly both with ordinary English usage and with the practice of recent writers on moral philosophy. The strategy of my argument is as follows: first, I stress a seeming paradox, namely that the use of evaluative expressions in general and that of moral terms in particular seems to presuppose impersonal standards in which rational men ought to be in agreement, but that in fact there is wide disagreement both among ordinary moral agents

about standards and among moral philosophers about the definition of morality. Secondly, I suggest that those two kinds of disagreement are closely connected and that rival concepts of morality imply rival contents for morality.

I then sketch two very different conceptions of what morality is. Depending upon which of these we adopt - if either - we shall mean two very different things by the words 'moral' and (in its wider senses) 'ethical'. One consequence of this is that 'moral' (or 'ethical') will point to quite different types of contrast with 'legal' in each case. Another is that there turn out to be two very different conceptions of the 'ethical' in the third and narrowest sense.

My entire argument embodies two distinctive negative contentions. The first is that it is impossible in our culture now to find a systematic way of using such words as 'ethical' and 'moral' which does not already embody not merely a particular morality, but a particular contentious morality which is at war with its rivals. The second is that because disagreements among moral philosophers parallel and reflect the disagreements among moral agents themselves - moral philosophers turn out to be merely the most articulate and systematic examples of moral agents - philosophy cannot as of now resolve these rivalries in any logically compelling way. The moral philosopher cannot indeed, I believe, avoid partisanship, although he must hope to be a fair and just partisan. Any notion of him as a neutral analyst who will merely dissolve confusion and unclarity, but not himself qua philosopher take sides (a viewpoint dominant for many years in the Anglosaxon world) is dangerously misleading. Part of fairness and

justice therefore is to warn you at the outset to be very cautious in accepting what I say.

Finally in the third section of the essay I consider certain aspects of morality which may be recovered independently of our stance on the wider disagreements. What I emphasize is the lack of homogeneity in what is so recovered. That is, I stress the disparate character of the different types of consideration which are perhaps misleadingly grouped together under the rubrics 'moral' and 'ethical.'

I

What makes a moral reason for doing this rather than that a moral reason? What makes a moral reason a moral reason? The two questions are inseparable and it is important to understand why. Begin with a lexicographical point. In English and other natural languages we can distinguish two quite different classes of expression which may be used to answer the question "Why should I do that?" The first type are sometimes called 'expressions of personal preference'. They include "I want to do (or have) that," "I prefer to do (or have) that," "I like...," "I approve..." and so on. Note that they are all in the first person. The second is the class of evaluative expressions - which includes distinctively moral expressions 'good', 'right', the adjectives of the virtues, such as 'just', 'generous' and 'courageous', and also 'beautiful', 'true', 'valid' and 'pleasurable'.

Consider a crucial difference in the import of these types of expressions when they are used to answer practical questions. I say to you, "Do such-and-such." You reply, "Why should I?" If my response to your question is of the form "Because I want you to" (or any other expression of personal preference), then I give you no reason for doing whatever it is independent of your relationship

to me. If you love me or hate me or fear me or are dependent on my good-will in some way (for example, I am your superior officer), then you have been given a reason for doing or not doing whatever it is; but otherwise you have been given no reason. (If an unidentifiable voice outside the room says "Do such-and-such" and you ask "Why?" and the voice answers "Because I want you to," the only question that will produce a reason for doing whatever it is, is "Who are you?") But with evaluative expressions it is quite otherwise.

If having said, "Do such-and-such," I respond to your question "Why should I?" by saying, "Because it would be right" or "Because it would be just," I purport thereby to give you a reason whose force is completely independent of my being the person who happens to have uttered it. The use of an evaluative expression is always to point to some criterion or standard of value, the authority of which is independent of the attitudes of both speaker and hearer. The meaning of evaluative expressions is such that if they are employed to give reasons in this way, then, if the reason is a good reason for action, it would have been so even if the speaker had never uttered it. Reasons which are expressions of personal preference depend upon the context of utterance for their force and authority; reasons which involve genuine evaluations do not.

It is important to stress that so far the point is purely a linguistic one. It is part of the distinctive meaning of evaluative expressions that they refer us to standards or criteria independent

of speaker and hearer; but what is referred to may not be there. It is the distinctive meaning of the word "unicorn" that it names a particular kind of animal; but there are no such animals. Nonetheless, the point is not unimportant. For it rules out of court immediately all those theories which have tried in one way or another to analyze evaluative expressions as disguised expressions of personal preference, attitude or feeling. It is still open to us to conclude that no evaluative reasons have any force or authority because there are no impersonal standards of value of the kind required; but if we do treat any evaluative - and more particularly - moral reasons as having force and authority, we shall only be justified in so doing if we have been able to vindicate the claims upon us of some impersonal source of authority.

Just this makes two features of our contemporary situation striking. One is the inability of moral philosophers even to agree on the meaning of the word "moral." In their useful anthology* G. Wallace and A.D.M. Walker list a number of possible defining characteristics of morality discussed by contemporary moral philosophers. Moral judgments, some have said, are necessarily universalizable: if I maintain that morally I ought to do such-and-such, then I am committed to maintaining that anyone else in relevantly similar circumstances ought to do the same. Moral judgments, some have said, are necessarily prescriptive; they are injunctions to perform certain actions and anyone who said "You ought to do such-and-such, but do not do it" - using "ought" in its primary moral sense - would be contradicting himself. Moral rules and principles, some have said, are just those rules

* The Definition of Morality, London, 1970.

and principles which are given overriding importance, or at the very least are necessarily treated as very important. Moral rules and principles, some have said, are those whose breach produces certain specific types of response and sanction: remorse or guilt in the agent, a particular kind of disapproval in others. And finally some have argued that moral rules and principles are those rules and principles which have a particular kind of content; they are concerned with particular kinds of harm and benefit.

Every single one of these theses has been asserted and argued for by more than one contemporary distinguished moral philosopher; every single one of them has also been denied and argued against by more than one such. I do not want to attend to the details of their disagreements, so much as to the fact of disagreement. For I take it that the inability of professional moral philosophers to resolve disagreement about the concept of morality and the meaning of such words as 'moral' and 'ethical' through argument is related to the inability of ordinary moral agents to resolve their disagreements about which moral principles are the correct ones. Consider two important contemporary moral debates.

I. A: A just war is one in which the good to be achieved outweighs the evils involved in waging the war and in which a clear distinction can be made between combatants - whose lives are at stake - and innocent non-combatants. But in modern war calculation of future escalation is never reliable and no practically applicable distinction between combatants and non-combatants can be made. Therefore no modern war can be a just war and we all now ought to be pacifists.

B: If you wish for peace, prepare for war. The only way to achieve peace is to deter potential aggressors. Therefore you must build up your armaments and make it clear that going to war on any scale is not ruled out by your policies. A necessary part of making this clear is being prepared both to fight limited wars and to go not only to, but beyond the nuclear brink on certain types of occasion. Otherwise you will not avoid war and you will lose.

C: Wars between the Great Powers are purely destructive and all of them ought to be opposed by revolutionaries; but wars waged to liberate oppressed groups and peoples, especially in the Third World, are a necessary and therefore justified means for destroying exploitation and domination.

II. A: Everybody has certain rights over their own person, including their own body. It follows from the nature of these rights that at the stage when the embryo is essentially part of the mother's body, the mother has a right to make her own uncoerced decision on whether she will have an abortion or not. Therefore each pregnant woman ought to decide and ought to be allowed to decide for herself what she will do in the light of her own moral views.

B: I cannot, if I will to be alive, consistently will that my mother should have had an abortion when she was pregnant with me, except if it had been certain that the embryo was dead or gravely damaged. But if I cannot consistently will this in my own case, how can I consistently deny to others the right to life that I claim for myself? I would break the so-called Golden Rule unless

I denied that a mother has in general a right on abortion. I am not of course thereby committed to the view that abortion ought to be legally prohibited.

C: Murder is wrong, prohibited by natural and divine law. Murder is the taking of innocent life. An embryo is an identifiable individual, differing from a new-born infant only in being at an earlier stage on the long road to adult capacities. If infanticide is murder, as it is, then abortion is murder. So abortion is not only morally wrong, but ought to be legally prohibited.

About these two arguments I want to make four major points. The first concerns the systematically unsettlable and interminable character of such arguments. Each of the protagonists reaches his conclusion by a valid form of inference from his premises. But there is no agreement as to which premises from which to start; and there exists in our culture no recognized procedure for weighing the merits of rival premises. Indeed it is difficult to see how there could be such a procedure since the rival premises are - to borrow a term from contemporary philosophy of science - incommensurable. That is to say, they employ and involve concepts of such radically different kinds that we have no way to weigh the claims of one alternative set of premises over against another. In the first debate an appeal to an Aristotelian concept of justice is matched against an appeal to a Machiavellian concept of interest and both are attacked from the standpoint of a Fichtean conception of liberation.

We have no scales, no set of standards, by which to assess the weight to be given to justice thus conceived over against interest thus conceived or liberation thus conceived. Similarly in the second debate an understanding of rights which owes something to Locke and something to Jefferson is counterposed to a universalibility argument whose debt is first to Kant and then to the gospels and both to an appeal to the moral law as conceived by Hooker, More, and Aquinas.

Secondly, in this unseizable character, in this use of incommensurable premises, these debates are clearly typical of moral argument in our society. If the debates had been about euthanasia instead of abortion or social justice instead of war, the characteristics of the arguments would have been substantially the same. Perhaps not all moral disagreement in our society is of this kind, but much is and the more important the disagreement the more likely it is to have this character.

Thirdly - and this is the point of my excursion into the characteristics of moral disagreement - there are crucial links between this kind of disagreement among ordinary moral agents over which moral principles we are to adopt and the current disagreements between moral philosophers about how morality is to be defined. Indeed one not uncommon type of argument used by contemporary moral philosophers has been of the form: if X's account of morality is accepted, then such-and-such moral principles would be acceptable; but those moral principles are precisely unacceptable, and therefore X's account of morality must be rejected. (Examples are G.E.M.

Anscombe on some Oxford moral philosophers in "Modern Moral Philosophy," (Philosophy, Jan. 1958), R.M. Hare on Max Black and myself in "The Promising Game" (in Theories of Ethics, ed. Philippa Foot, Oxford, 1967), Beardmore on Philippa Foot (in Moral Reasoning, London, 1969). Appeals to one's own interests of the kind that appears in B's argument in the first debate are precisely not universalisable; appeals to a law that exists independently of our apprehension and endorsement of it, as in A's argument in the first debate and C's in the second are precisely not prescriptive ; B's argument in the second debate does not concern itself with specific kinds of harm and benefit in the way that some have considered essential to morality; and all these attempts to discriminate between some of these arguments as belonging to morality and others as not would fail in the eyes of those for whom morality simply consists of those principles which their protagonists take to be overriding.

There is of course no simple and easy conceptual connection between defining morality in one particular way and holding some particular set of moral principles; the connections are complex and sometimes indirect. Nonetheless a thesis has emerged: that the conflict over how morality is to be defined is itself a moral conflict. Different and rival definitions cannot be defended apart from defending different and rival sets of moral principles.

This conceptual connection between the content of moral principles and the definition of morality will perhaps be best elucidated by considering its historical explanation. When I characterized the rival moral premises of contemporary debate as Aristotelian, Machiavellian, Fichtean and so on, I suggested something of the wide range of historical

sources on which contemporary moral argument draws, but I did so by using the names of philosophers as a kind of allusive shorthand. Three points need to be made in a more extended way. The first is that the origins of contemporary moral debate are not to be found only or even mainly in the writings of philosophers, but in the forms of argument which informed whole cultures and which the writings of philosophers articulate for us in exceptionally clear and accessible ways: Aristotle is being treated here as a spokesman for at least a central strand in the culture of fourth century Athens, Fichte as related in a similar way to nineteenth century Prussia.

Secondly, the premises of contemporary moral debate have not merely been inherited; they have also been torn from the social and intellectual contexts in which they were originally at home, from which they derived such force and validity as they possess. What we have inherited are only fragments and one reason why we do not know how to weigh one set of premises against another is that we do not know what force or validity to grant to each of them in isolation.

Thirdly, as the conceptual connection between the content of morality and its definition would lead us to expect, this fragmented inheritance is embodied in our rival definitions of morality as well as in our rival sets of moral principles. The extent to which this is so will not be entirely clear from my initial summary of Wallace and Walker's anthology; for they restricted themselves to the views of one particular school of moral philosophers, those in the analytical tradition which has dominated most Anglo-American philosophy in this century. Yet there was some point in citing their anthology; for if

even philosophers who are all of the same philosophical cast of mind to a large degree cannot agree on the definition of morality; then much more widespread disagreement can be expected among philosophies of different schools. And is to be found.

Fourthly, the central problem can now be set. I argued at the outset that the peculiar function of evaluative expressions in our discourse is to refer us to impersonal standards of value, to give reasons whose force is independent of who utters them. The implication is that in this part of our discourse we ought to be able to arrive at rational agreements on central, if not always on peripheral, issues. Yet the state of moral argument in our culture shows this not to be so. We therefore seem to be in a dilemma: either we have to reject the presuppositions of the dominant culture of our own society or we have to reject the possibility of rationality in moral argument. But the roots of this dilemma are, so I have suggested, historical. It may therefore be worth asking for a somewhat longer account of those roots in order to understand what is involved in the dilemma.

II

The United States is the only known political society whose self-avowed basis is assent not only to a particular set of highly debatable moral judgments, but to an even more debatable philosophical theory about the character of these moral judgments. Belief in self-evident truths about equality and rights to life, liberty and the

pursuit of happiness require some very cogent philosophical basis. Jefferson himself was clearly to some degree aware of this for he cites as the sources of his thought in the Declaration both the "commonplaces" of his own age and the writings of four philosophical theorists - Aristotle, Cicero, Locke and Algernon Sidney. What Jefferson does not remark upon is the not merely heterogeneous, but even mutually antagonistic character, of these philosophical sources. The moral scheme represented by Aristotle and the moral scheme represented by Locke may consistently both lack rational warrant, but they cannot both possess it, for the truth of the one entails the falsity of the other. The prospect looms: the United States is perhaps founded upon a moral contradiction. If so, unclarity about what constitutes a moral consideration may be central to our political culture. Perhaps to be clear and coherent in this area is necessarily to be un-American. Perhaps - but we need to explore further. To do so I am going to ignore some of the stands in our moral culture which I have already noted - the German Fichtean one, for example, and concentrate upon the two suggested by Jefferson, although I shall not tie myself specifically to the details of the thought of Aristotle or of Locke. Instead I shall more generally delineate what I shall call the classical view of value, a view shared in substance if not in detail by many ancient and medieval thinkers, and the modern individualist view. What we have inherited are parts of both and the whole of neither and from this, I shall argue, derives the central incoherence in our view of what constitutes a moral consideration.

On the classical view there is no concept of morality as we distinctively understand it. There is indeed no word in classical or medieval Greek or Latin which can be translated by our word moral. It is true that our word moral derives etymologically from the Latin moralis and that Cicero invented moralis to translate the Greek ἠθικός, the etymological ancestor of our word ethical. It is also true that Liddell & Scott's Greek dictionary gives moral and ethical as translations of ἠθικός. But it errs and etymology turns out to be a bad guide to translation. ἠθικός means having to do with character and a man's character is the sum total of his dispositions to act in determinate ways. Aristotle's Ethics is about practical life in general. The excellences of character which he describes go far beyond the limits of what most modern writers take to be morality.

Moreover for Aristotle ethics as a subject of enquiry is subordinate to politics. But what he means by 'politics' is as different from what we mean by 'politics' as what he means by 'ethics' differs from what we mean. Politics is the enquiry into the proper form of the polis - and we cannot translate polis by city-state if that suggests to us the kind of contrast between the state on the one hand and the community on the other which is central to political thought in our sense of 'politics.' The polis is the community and the state, understood as one, not two.

The basic concept in the classical moral scheme is that of the good for man. Men are conceived of as having an essential nature informed by a τέλος, an end, movement towards which completes and fulfils that nature, failure to achieve which frustrates and disappoints. The human good is such that men cannot achieve it in isolation; it is only as members of a community that men can achieve their good.

Hence the basic split between self-interest and altruism which figures so prominently in modern moral thought is absent. I am incomplete, not fully human, without others - my friends, my kin, my city. Philoctetes, in Sophocles' play, describes himself as having been rendered by enforced isolation on a desert island "without friends, desolate, without a polis, a corpse among the living," and this is in no way intended as a rhetorical exaggeration. Without sharing it with others, there is no good to be achieved by man; hence Aristotle's argument that one cannot be a good man without being a good citizen.

What the good for man is is to be determined by rational argument. There are of course many goods in human life and each of them is a characteristic object of human desire: health, knowledge, honor, prosperity, pleasure and so on. The good for man is that form of life in which each of these goods have their due place; 'happiness' is the name given to enjoyment that accompanies and is internal to the activity of leading that form of life. 'Happiness' then is not, on the classical view, the name of a separable psychological state. It does not stand to the activities which it accompanies as end to means, or as byproduct to achievement, or in any kind of purely contingent relationship. The-happiness-of-climbing-a-mountain or the-happiness-of-playing-tennis-well are not psychological states superadded to the activity of climbing a mountain or of playing tennis well; they simply are these activities as they are enjoyed by one fully engaged in them.

Human excellences or virtues are those dispositions which enable a man to achieve the good. A crucial excellence is that of

friendship. From the modern point of view it is odd to discover friendship in the same list of the virtues that includes courage, generosity and justice. But friendship is on the classical view a necessary part of achieving the good; indeed friendship provides the true form of relationship both between citizens and between kin. Although friendship will characteristically involve what we shall call affection and other psychological states, it is primarily a matter of commitment and it is the precisely defined character of the commitments which ensures that friendship itself is a precise notion. Consider by contrast how loose and imprecise the notion of friendship has become in our own culture.

The virtue of justice in the classical scheme presupposes the general applicability of a concept of desert, of what is due to each kind of person and to each person. Desert is in part a matter of the place of each kind of person in the life of the polis and in part of the past behavior and achievement of individual persons. Justice is the first virtue of a community because without a just sharing of goods and apportioning of punishments the common pursuit of the good for man will not be served.

I have picked out the virtues of friendship and of justice for special attention because we too possess conceptions of friendship and of justice, but the dominant conceptions amongst us differ markedly from the classical ones; and this is more likely to bring out the nature of the difference between the classical scheme and its modern successors than is attention either to those virtues

where our own view and the classical is much closer - as in the case of courage - or to those classical virtues, such as great-souledness of which our culture scarcely has any conception. But all the virtues in the classical scheme have the same function; their cultivation is to result in putting human desires into an order so that in seeking what we want we shall achieve and not frustrate our human nature. Our desires and emotions pull us in many directions initially and especially when we are young; moral training is a matter of guiding them and redirecting them, so that we avoid destructive excess in any particular aspect of life. But it is wrong to read such classical maxims as "Nothing in excess" as merely negations in their intention. There is no ultimate contrast in the classical scheme between morality and desire, as there is in some later schemes - the Kantian for example. Indeed it is through moral training that we learn to fulfil desire, but in a distinctively human way. Those who insist on setting no limit to any one of the desires do not make themselves happy, but become slaves to that desire - and they destroy the community of the polis. The name for this vice is πλεονεξία (pleonexia).

What one has to learn therefore is judgment: how to exercise the relevant virtues in a particular situation. This capacity is itself a virtue, the virtue of prudence. The capacity for judgment in the classical sense goes strikingly undiscussed by modern moral philosophers. They have tended to suppose that moral reasoning is either a matter of skill in designing the means to achieve a given end or a matter of bringing a particular case under a general rule.

Indeed commentators on Aristotle's account of practical reasoning have characteristically misread it, by reading into Aristotle a modern view of such reasoning and not seeing there what is distinctive and unfamiliar. Modern moral philosophers, like modern moralists, tend to lay a great emphasis upon rules. This emphasis is absent in the classical scheme, for in that scheme it is held that in crucial and central cases where moral judgment has to be exercised the accepted maxims of morality by themselves will yield no answer (just as for a judge the crucial precedent-setting cases of judgment are those in which the accepted laws by themselves give no answer).

Finally it should now be clear that the presuppositions of the whole classical scheme is both that men are able to and do achieve rational agreement in what the good for man is and on how it is to be achieved and that men are capable of governing themselves both individually and collectively by reason. This view of man's essential nature is perhaps what divides us most strikingly from our classical ancestors. For it is not just in our moral transactions, whether theoretical or practical, that we presuppose the untruth of the classical view of human nature; it is also in the whole range of the human sciences. Whatever the wide range of disagreements in such disciplines as sociology, psychology and anthropology they agree - and have agreed since the eighteenth century - in rejecting any classical and more particularly any Aristotelian view of man. This agreement does not by itself settle anything; for in order for us to be rationally influenced by it we should have to ask whether it results from the findings of those sciences or from assumptions that

their practitioners have made prior to these findings which result in them interpreting what they learn in one way rather than another. But whichever of these alternatives holds, the fact remains that the classical view is massively inconsistent with a great deal that almost everybody now believes. At the same time we have inherited a large portion of our moral vocabulary from the classical view. For the classical view comes down to us not only from the Greeks, but as mediated by various forms of theistic classicism - Christian and Jewish Aristotelians and Platonists of a variety of kinds. Of course I have therefore oversimplified in speaking of the classical view; but at least the oversimplification has provided some conception of a perspective which was once near universal in cultures that are among the ancestors of our own.

The same complaint of oversimplification may with equal justice be made against the sketch of modern individualism with which I now want to complement my account of the classical view. Let me begin from two starting points. The first is that the concept of rights - which we take for granted so easily - only emerges in the modern age. There is no expression correctly translated by our expression "a right" in either classical or medieval Latin or Greek or Hebrew, and in this we may note it is Latin and Greek and Hebrew and not modern English or French which speak for the majority of the human race. There is no expression in Japanese, for example, correctly translated by our expression "a right" until nineteenth century liberal Japanese political writers invented one. It is an interesting paradox that those eighteenth century writers such as Jefferson or Robespierre

who believed that they intuited timeless truths about the rights of man did so in a vocabulary that had historically come into existence as a child of late medieval legal usage and which does not seem to be found in the precise senses in which they used it until a hundred and fifty years or so before their own time. But it is easy to understand why it did emerge as a central moral as well as legal concept. The central preoccupation of both ancient and medieval communities was characteristically: how may men together realize the true human good? The central preoccupation of modern men is and has been characteristically: how may we prevent men interfering with each other as each of us goes about our own concerns? It is interesting that when John Stuart Mill translates pleonexia he mistranslates it as "the desire to engross more than one's share of advantages" - the best modern translation is Nietzsche's "mehrundmehr wollen haben" - for this is yet more evidence of the way in which the individualist view throughout its history assimilates other conceptual schemes to its own by misinterpretation and mistranslation and thereby presents itself as though it were morality as such.

The classical view begins with the community of the polis and with the individual viewed as having no moral identity apart from the communities of kinship and citizenship; the modern view begins with the concept of a collection of individuals and the problem of how out of and by individuals social institutions can be constructed. The isolated, autonomous individual is in classical Greek social thought the pathological specimen - Thrasymachus in Plato's fiction and Alkibiades the traitor in fact to both his own city and to Greece

were as pure an example as any; for modern morality we begin from just such an individual as the fundamental unit of moral and social thought and practice. We may notice that the word "individual," used as I have been using it, is itself a linguistic innovation in the period which marks the origins of modern morality. Until the seventeenth century the word "individual" is almost exclusively a technical term of logic, contrasted with the word "class," another technical logical term which is about to acquire a social meaning. Its predecessors are "man" and "person". "Man" in its Greek and Latin synonyms is both biological and social; "person" emphasizes role-status. What matters is the systematic character of the linguistic invention necessary to make both the modern moral vocabulary and modern moral theory possible.

How can a society or a morality be constructed out of a set of individuals? The answers are different in different philosophical authors: Hobbes has one view, Locke a second, Diderot a third, Hume a fourth, Adam Smith a fifth. But every one of these authors faces in the context of his own distinctive theory one and the same problem. For each of them sees the institutions of social and political life as external to the basic projects and purposes of individuals who are each moved by their own desires. The notion of a common good which is the object of each man's true desire has disappeared. The extent and the direction of individual self-interest is differently assessed by different authors. Hobbes does not agree with Locke, Hume in the Enquiry does not agree with himself in the Treatise and Diderot was capable of radical disagreement with himself within the pages of one and the same book. But however they characterize self-interest their

problem is: how can the authority of moral rules or that of social and political institutions be the outcome of the coming together of basically self-interested individuals? The answer in these authors is psychological. Human nature must have some other original component which mitigates and modifies what would otherwise have been the effects of self-interested desire. In Hobbes it is the mutual fear of death at each other's hands, in Hume it is a larger view of our own interests reinforced by sympathy, in Smith an original capacity for sympathy is the mainspring of morality. But what matters is not the contrast of the solutions (every one of which fails), but the form of the problem. For it is the form of the problem which dictates the content of morality. Morality concerns that arrangement of social rules which prevents my preying upon you and vice versa; morality therefore is a form of restraint upon our desires, and both morality and social institutions are means to a further end. They are instruments designed to enable us to achieve fulfilment of some of our desires by sacrificing others. Hence the content of morality becomes essentially a set of prohibitions framed as rules. The further question at once arises; in what circumstances, if any, may we make exceptions to the rules?

One striking fact about the moralists of the eighteenth century, in France, England and Germany is that they are in fact highly conservative about the content of morality. With minor exceptions they accepted the inherited set of rules, but understood them in a new individualist way. But in accepting the inherited set of rules, they accepted rules whose form was unamenable to understanding in the new

way for a reason on which I have so far touched only in passing. Jewish, Christian and Islamic theology all inherited and nurtured within themselves versions of the classical view of morality. But they all added to it another set of elements. Man indeed has a desire for his true end, even if that desire is corrupted by sin. Man's natural rational morality is therefore congruent with divine law since God created man to achieve his end by obeying that law. But in his revelation in the scriptures God has set forth his law directly; to the injunctions which spring from the virtues the form and the authority of laws has now to be given. It is of the essence of these laws that being divine they are unconditional, that is, they admit of no exceptions and this character of unrestricted universality and generality is written into the form of the theistic moral rules. When these rules are inherited by seventeenth and eighteenth century thinkers, they at once encounter problems. We are to obey the rules of morality because they restrain some of our desires and so enable us to fulfil others. But what if on particular occasions continuing to obey the rules will not serve the fundamental purpose of morality at all? What if on this occasion breaking the rule will serve my interest? What if on this occasion breaking the rule will serve the interests of a number of people and harm nobody? Are there not occasions on which we should break rather than keep promises, tell lies rather than the truth?

We find therefore in the individualist account of morality a number of elements which are not entirely coherent with each other. Morality

is to protect the invasion of my and your rights by others;
morality is to be the expression of my and your fundamental interests;
morality is to be a set of unconditional universal rules; morality
has no source but the will of each individual; morality is
essentially negative, a set of restraints on otherwise anarchic
and conflict-engendering desires. Confronted with these not entirely
compatible theses, which are increasingly embodied in the public and
private transactions of the seventeenth and eighteenth century, moral
philosophers responded by trying to impose consistency, often in the
name of some epistemological ideal or some view of human nature.
Kant, accepting both that the individual utters the moral law to
himself and that that law is expressed in universal and unconditional
rules, rejects the notion that moral rules are in any sense expressions
of our desires. Consistently he explains moral rules as an expression
of reason whose relationship to inclination is at best one of
neutrality, often one of constraint. Duty and inclination are to
be viewed as totally distinct. Smith by contrast constructs a
compromise between sympathy and self-interests; whereas the
utilitarians, rejecting any basis for morality except a psychological
one, find it difficult not to treat rules as rough and ready in-
structions on how to get as much as we can of what we want without
frustrating and being frustrated by other pursuers of desire.

We can already recognize in these mutually incompatible attempts
to articulate moral individualism into a consistent scheme part
of the ancestry of the rival contemporary accounts of what morality
consists in summarized by Wallace and Walker. Universalisability,

prescriptivism, and the view that morality is defined by its subject-matter all have eighteenth century origins. Their detachment from their origins has led their protagonists to make claims for them as timeless, distinguishing marks of universal morality, rather than as historical survivors from particular phases of moral history, a phase itself marked both by incoherence and by a blindness to the existence of its most important conceptual rival, the classical view of morality.

The conclusion which I suggested earlier is then reinforced and expanded by this abbreviated history: rival accounts of what morality is presuppose rival moralities and there is no way of deciding upon the truth or falsity of the claims of any particular account of what morality is or what we are to mean by 'moral' without deciding upon the truth or falsity of the claims of the relevant morality. We may well flinch from this conclusion because of the enormity of the task which it seems to impose upon us. But in fact the situation is even more difficult than I have suggested so far. For it turns out that there are morally different ways of flinching, morally different ways of responding to this situation.

III

The heirs of modern individualism have to recognize not only their shared differences from the classical tradition, but also their shared inability to agree with each other. They are apt to conclude

either that there is no such thing as the good for man or at the very least that rational agreement on its character has to be ruled out. Sir Isaiah Berlin writes that "the highest ends for which men have rightly striven and sometimes died are strictly incompatible with one another...Even if, per impossibile, we could choose among these ideals, which should we accept? Since there is no common standard in terms of which to grade them, there can be no final solution to the problem of what men as such should aim at" (Vico and Herder pp. 211-212) and although Berlin is expounding the thought of Herder, it seems clear that he is also endorsing it. When John Rawls describes the way in which we ought to envisage the terms of an original contract between individuals on which a concept of justice might be founded, he says of those individuals that they "do not share a conception of the good by reference to which the fruition of their powers or even the satisfaction of their desires can be evaluated. They do not have an agreed criterion of perfection that can be used as a principle for choosing between institutions. To acknowledge any such standard would be, in effect, to accept a principle that might lead to a lesser religious or other liberty..." (A Theory of Justice, p. 327). Daniel Bell attacks adherents of the classical view, of Catholicism and of Communism as sharing a doctrine whose effect is "to fuse law and morality, to insist that there is a single overriding principle..." and quotes Berlin in support of moral pluralism. Berlin, Rawls and Bell are interestingly different witnesses to the strength of the same position; each sees the classical view of morality as not merely false, but

threatening. Each sees agreement on the good for man as something that would necessarily be imposed rather than rationally shared.

We therefore have on their view to separate law from morality and to separate that portion of morality which is necessary to underpin law if individual autonomy is to be safeguarded and its rights acknowledged from any particular concept of the good for man. There must be one part of morality which is private, various and reserved for moral pluralism; there must be another which is public, and where agreement can be secured without being imposed.

The classical view of morality does not allow for this division of morality: law is to be at once the servant and the expression of morality. The law is not merely an instrument to prevent one man interfering with another to that other's harm; it is the community's assertion to itself and to other communities of what it values and of one means of achieving the good. It certainly does not follow from this view either that everything held to be immoral ought to be made illegal or that those who hold contrary views of morality ought to be legally penalized. (Liberal thinkers such as Bell, Talman and Berlin have often asserted a causal connection between totalitarianism and some version of the classical view of man; but I would want to contend that this is a highly dubious historical thesis. The roots of totalitarianism lie elsewhere). But it does mean that the contrast law/morality appears quite differently in the individualist perspective for the way it appears in the classical perspective; and this marks one further variation in, one further fragmentation of the concept of morality.

The classical perspective, with its demand for civic virtue, experienced a certain rebirth in the middle and late eighteenth century in the form of the revival of Greco-Roman and Italian republican ideals. It coexists uneasily with individualism and it is a clue to the ideological structure of the age that the conflict between these two points of view largely went unrecognized. We have already noticed this lack of recognition in Jefferson; it could easily be paralleled in Robespierre and in many other lesser writers. But this lack of acknowledgment is not restricted to the eighteenth century. It is still at work unrecognized in contemporary argument where what at first sight appear local and particular disagreements often mark just this large rift between two rival total conceptions of morality. Consider one particular case of just such a disagreement.

As I noted at the outset, the word 'ethical' has acquired a special use in connection with professional standards. Within the history of professions we can distinguish two quite different ways of envisaging unethical conduct and they are in turn linked to two rival conceptions of the character of a profession. One of these lays primary stress on autonomy as the key characteristic of a profession. In virtue of their shared exclusive possession of certain skills, the members of a profession are licensed by government to adjudicate on the legitimate use of these skills. The public is entitled to ask that the profession maintain standards; but it would infringe autonomy for the community through government or any other agency to say what these standards are to be.

By contrast there is an alternative conception which begins from the classical notion of society as a community in which certain goods

are recognized as shared. Each good has its due place and because each good cannot be pursued by everyone equally the community entrusts the pursuit of particular goods to particular groups of people: the goods of health and life to the doctors, the goods of national independence to the military, the goods of rational enquiry to schoolteachers and professors. A profession is just a group to whom a special concern with one particular type of good has been entrusted. Hence there is an obligation laid on that group to cultivate and promote the skills necessary for achieving the good in question. The autonomy accorded to a profession by the wider community is a mark of the trust placed by the community in that profession. It is in virtue of this agreement upon goods and this trust that members of the professions are accorded a type of authority and respect which goes far beyond anything that could derive from the mere possession of skills. The authority of physicians is perhaps the most obvious example; but lawyers, professors, clergymen and others have in the past at least shared in it.

What has happened unfortunately is that this public agreement on goods presupposed by this conception of a profession has been replaced by moral pluralism and hence the concept of autonomy has become primary instead of secondary. Hence professional standards lose their original connection with more general beliefs about man and society and 'ethical' takes on its special use. The claim to autonomy becomes an assertion of a right rather than a sign of trust, a right of each profession to declare what is or what is not 'unethical.'

'Unethical' then always has reference to professional standards, but it has been used to refer indirectly to more general standards in virtue of which professional standards are to be vindicated. Once again rival uses imply rival moral standpoints.

IV

Finally I return to the metaphor of fragmentation. The range of disagreements which I have characterized has left us not with a single unitary code or set of ideals, but with a set of fragmented and often conflicting beliefs and concepts. Often conflicting, however, but not always; and not all the fragments we have inherited are of the same kind. We therefore can set ourselves the task of distinguishing between what can be rescued from our moral history and what cannot, what may survive all disagreement and what certainly does not. I shall deal in turn with four concepts: those of a virtue, a good, a right - and more surprisingly perhaps - of a stranger. I shall argue that we can rescue something important from the notions of a virtue and a good, that the concept of rights is so gravely damaged as to be unusable except in a legal sense and that the concept of a stranger has for us something of the importance which it had in Homeric times.

Begin then from the concept of a virtue. At first sight this may seem a concept rendered almost unusable by the range of disagreements concerning it. It is notorious that in different times and places not only have different lists of the virtues been given, but that different concepts of the virtues have been employed. Aquinas following the Christian gospels treats humility as a virtue, Aristotle treated it as a vice. Kant held that the very notion of virtues (in the plural) was a confusion. And here once again

philosophers are representative voices of the wider culture. Nonetheless, there is a core to the concept of the virtues and there is a set of core virtues the acknowledgement of whose authority over us is presupposed in any characteristically human set of transactions. These are the virtues in terms of which we define our relationship to each other whether we will it so or not. Consider the case of truthfulness and imagine the situation of three friends who have all been disturbed by and concerned over the disappearance and obscure death of a fourth mutual friend. A takes the trouble to discover precisely how and in what circumstances D died; A then tells the truth about D's death to B, but lies to C. In so doing A has inescapably defined his relationship to C as crucially different from his relationship to B. A may intelligibly elucidate this difference further in a number of different ways: he wished to protect a fragile and anxious C, but considered B robust enough to endure the truth; or he wished to protect D's reputation from gossipy C, but not from discreet B; and so on. But A has defined C as having inferior standing to B in his life in some respect and this he cannot intelligibly deny. The norms of truthfulness provide the background in terms of which we interpret the attitudes of others to ourselves and our own attitudes to them. As with truthfulness, so also with fairness and courage.

If in distributing rewards for merit or punishments for offences I use any criteria other than those of merit and demerit

- for example, I give the highest grade not to the student who wrote the best examination, but to the student with bluest eyes - I thereby define my relationship to the students as other than that solely of teacher to taught and it is by violating the canons of fairness appropriate to the situation that I have done this. With courage the matter is a little more complex. Courage is a virtue because of the connection between caring for a person, a group, an institution or an ideal and being prepared to risk harm or danger on their behalf. The standard test for whether or how much I care or am concerned is precisely what degree of discomfort, pain or trouble I am prepared to endure to achieve the good of whoever or whatever it is. So we define our loves, affections and loyalties by our will to endure; and without the implicit acknowledgement of courage as a virtue they could not be so defined.

The virtues of truthfulness, fairness and courage are of course embodied in very different codes in different cultures; but this difference in codes is perfectly compatible with their functioning with the same impersonal authority as defining notions in all those cultures. Where we find a society, such as that of the Ik, in which the authority of these virtues goes quite unrecognized we also find a society lacking many other distinctively human characteristics; it is in fact necessary to characterize the Ik in terms of absence and loss, the absence and loss precisely of the core virtues.

The concept of a virtue functions in our evaluations very differently from that of a good. To elucidate the latter concept it is important from the outset to distinguish what I shall call external and internal goods. Some goods are internal to a given form of human activity of practice. Example of such practices are mathematical

enquiry, agriculture, the common law and the game of chess. A small child may originally learn to play chess because he or she is being rewarded with candy both for playing at all and for playing with increasing degrees of skill. So long as the child is only playing chess to get the external good of the candy, so long the child has no reason to excel at chess rather than merely to give the appearance of excelling at chess. If, by cheating at chess, the child can obtain the candy more or as easily than by playing chess well, the child has indeed a good reason for cheating. External goods are related to the activities which produce them as end-products to means and economy of means is always rational. But when the child comes to appreciate chess as an activity in and for itself, when the child comes to desire those goods internal to chess-playing, then the child by cheating merely frustrates him or herself. For the child can only achieve the goods of chess-playing by playing well. An internal good is not an end-product of its activity; it is achieved in carrying the activity through to a successful completion.

Many activities have both internal and external goods. Agriculture as a mode of productive life in which man is related to nature in a highly specific way has its external goods; but it also produces turnips and money. Tennis is a game which like chess has its internal goods; but it also produces health and sometimes money and reputation. Yet external goods are always liable to corrupt participation in any activity, while internal goods are not; and those who participate together in an activity for the sake of the internal goods have a

quite different moral relationship from their relationship to those who merely service or provision the activity in some way in return for external rewards.

Judgments about virtues and judgments about goods are incorporated by Aristotle and by many classical moralists into one overarching scheme. But it is crucial to notice that, in the absence of any overarching conception of the good for man, judgments about virtues and judgments about goods are logically independent of each other. This is not just because they are judgments about different subject-matters, virtues being qualities of individual agents' character and goods being the end of activities and practices. For under certain circumstances - circumstances which arise often enough in our contemporary social world - virtuous moral agents may destroy good and produce evil, while men notably lacking in virtue may in fact achieve and create notable goods.

It is just this type of situation which makes it practically tempting to invoke the notion of rights, but also both theoretically and practically dangerous to a degree. For when the authority of the core virtues and the authority of certain goods are as unrelated as they are, we may well conclude that promoting excellence and avoiding harm are not very closely connected. Virtues and goods are aims of excellence; but if we are to avoid doing injury and damage we need an additional and independent source of guidance - rules that will constrain and prevent rather than enable and promote. It is in the concept of a moral right that we are often tempted to search for a foundation for such rules of negative constraint. But there is a

fatal objection to doing so.

This is the arbitrariness of all claims to rights. This arbitrariness emerges clearly if we ask precisely what rights all human beings possess, a question to which both the American and the French revolutions professed to give an answer. To life, to liberty, to happiness - to property, to a job, to a fair trial ... what criteria qualify for inclusion in the list, what for exclusion? The arbitrariness emerges once more if we ask under what conditions each of our alleged rights is defensible. When right clashes with right or with the public interest or with the greatest happiness of the greatest number which is to give way to which? We only do not drown in a sea of uncertainties by resorting to fraudulent assertion and counter-assertion. Note that I am not suggesting that all claims to moral rights at all times are arbitrary and unfounded - that was Bentham's view. But claims to right have only not been arbitrary when they have been asserted in specific historical contexts in which a good was in danger of being sacrificed by an infringing power. The claim to a right is then essentially negative in form. The agents of the infringing power are told that they have no right to deprive us of some good. The inference is from a premise of the form "X has no right to deprive us of such-and-such a good" - a premise to be established in turn by sceptical arguments - to a conclusion of the form "Therefore we have a right to enjoy it." This was the form of the claim in which the case against general warrants was argued both in English and in Massachusetts courts in the eighteenth century. But this intelligible, rational, context-bound claim was then generalized by

Jeffersonian philosophy so that the claim to natural rights is no longer a conclusion derived from premises - but a somehow underived claim.

It follows that considerations about rights are very different in their rational force from considerations about either virtues or goods; they may indeed have such force, but only in certain types of context. If we insist on invoking rights outside such contexts we shall misuse the notion in such a way that something like C.L. Stevenson's emotive theory of moral judgments will become true; claims to rights will function as mere expressions of personal preference, of attitude and emotion. The immediate result will be to substitute assertion and counter-assertion for argument; the next consequence most probably to discredit this form of discourse altogether. (There are signs that this is already happening). Is there then any other concept available to us in specifying the kind of restraints on possible harm-producing acts which we need to accompany any pursuit of goods and cultivation of virtues?

In the society reflected in the Homeric poems and in that reflected in the Icelandic sagas - both earlier predecessor cultures of our own - a crucial concept is that of the stranger. Both societies, unlike our own, were made up of small communities in which everyone occupied a clearly determined role, with both kinship and social relationships specified as sets of mutual obligations. How to act and react in relation to other members of the same community was in such a society largely unproblematic, but the question obviously arose of how to react to the stranger who arrives in or passes through the community and who possesses no allocated role. About the stranger men do not know

whose kin he is or what his status may be and they cannot usually verify what he tells them; nor do they know what goods he pursues or what virtues or vices he possesses. They are not participants in common activity with the stranger. All the cues that they normally need to guide their responses are missing. They therefore have to have a special code for this type of case.

Note that in such societies men do not treat strangers as they do because of any phantom notion that strangers have rights. It is because they themselves could not consistently pursue the goods which they seek, or cultivate successfully the virtues to which they aspire if they did not show a special kind of concern for strangers, a concern embodied in rules enjoining hospitality and safe-conduct, for example. When Odysseus comes upon the Cyclopes the key test of whether they are civilized men or not is whether they exhibit themis (a custom- and rule-governed attitude) towards strangers. (The Cyclopes, it turns out, eat strangers).

But what relevance can this concept, torn from its place in Homer and the sagas, have in a society as different as ours is from theirs? The answer is that in a crucial sense the relationship of most people in our society has become that of strangers to strangers. It was not so in the rural and small-town America of late eighteenth and nineteenth century America. But we outside our homes, our places of work and our immediate neighborhoods are essentially strangers who have learnt to meet each other with something of the same suspicions that Odysseus had of the Cyclopes (eating strangers can take a variety of forms). It is precisely a claim about the incompatibility of treating

others who are not participants in the same forms of activity as objects for our consumption with our own pursuit of virtues and goods which is embodied in the Homeric and Icelandic concept of the stranger (the same word is used of both guests and strangers in Greek).

It is not just then that the surviving fragments of morality are various and variously usable. It is also the case that if we wish to use them it matters in what order we move from one to the other. We can defend the virtues on one basis, the goods that we pursue on another; but unless we already have provided a rational account of those virtues and goods we prize, we shall have no basis for invoking any such concept as that of the stranger. But without such a concept we shall be at a loss how to act in many types of situation.

What I am saying amounts to this: because what we have inherited are a variety of fragments - sometimes mutually inconsistent and some of them unusable by those committed to rational argument - we cannot as philosophers content ourselves with the task of analysis. If we did so, our reply to a request for an account of the concept of morality, of the meaning of 'ethical', would have to be: there no longer is such a concept or such a meaning. Instead we are forced into a task of conceptual reconstruction. Any such reconstruction will, as I suggested at the outset, itself be morally partisan. Philosophers can no longer be comfortable in the claim that they are only exhibiting in clear form the contents of the ordinary agents' moral consciousness. If the view that I am urging is correct, then it will be true that ordinary agents who believe that they already

possess a well-educated moral consciousness - as most people do - are generally going to be people with a corrupted and deformed moral consciousness. Hence this account, if true, ought to be unpopular. A necessary condition of my arguments being acceptable by any is that they should be rejected by most.

11

SOME ETHICAL ISSUES IN RESEARCH INVOLVING
HUMAN SUBJECTS

LeRoy Walters, B.D., Ph.D.

SOME ETHICAL ISSUES IN RESEARCH
INVOLVING HUMAN SUBJECTS

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"The Commission shall...conduct a comprehensive investigation and study to identify the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects...."

-Public Law 93-348

Summary: This essay is divided into an introduction, the main body of the essay, and a conclusion. The introduction defines terms and delimits the scope of the essay. In the main body of the essay seven major ethical issues are discussed: (1) the moral justification for nontherapeutic research involving human subjects; (2) research design; (3) risk-benefit analysis; (4) the selection of subjects; (5) informed consent; (6) the social control of research; and (7) the compensation of injured research subjects. The conclusion attempts to synthesize the ethical principles which have emerged from the preceding discussion.

Introduction

Human research (or human experimentation) can be defined as planned manipulation, observation, or study of one or more human beings which differs

in any way from customary professional practice.¹ Within the biomedical realm three subcategories of research can be distinguished: (1) therapeutic research, in which the design of the activity or procedure is solely to benefit the patient -- whether by prevention, diagnosis, or treatment; (2) nontherapeutic research, in which the design of the activity or procedure is solely to gain new knowledge; and (3) mixed research, in which the design of the activity or procedure is partially to benefit the patient-subject and partially to gain new knowledge.² This essay focuses on nontherapeutic research and mixed research, that is, on research in which the therapeutic/nontherapeutic ratio is less than 100/0. For the sake of brevity, the term nontherapeutic research is used throughout the essay as a shorthand expression for the more cumbersome phrase "nontherapeutic and mixed research"; both patient-subjects and subjects are referred to simply as "subjects."

The primary emphasis in the essay is on biomedical rather than behavioral research since a more clearly defined ethical tradition and a richer ethical literature exist for the biomedical sphere. However, many if not all of the ethical principles developed in the essay are also applicable to behavioral-research activities.

The method of the essay is to analyze seven major ethical issues in human research with a view to identifying one or more ethical principles which are pertinent to each issue. Four of the issues -- risk-benefit analysis, the selection of subjects, informed consent, and social control -- are derived from the charge to the National Commission in Public Law 93-348. The issue of research design is closely related to risk-benefit analysis and the selection of subjects. The remaining two issues seem to the author to be of comparable significance. They raise the questions: Should nontherapeutic human research be performed at all? and, What debt, if any, does society owe to injured research subjects?

At the beginning of each section relevant portions of three major codes of research ethics will be quoted. These quotations from the Nuremberg Code, the Declaration of Helsinki, and the 1974 DHEW Guidelines will serve to indicate how much attention major traditional codes have devoted to the various issues and will provide a point of departure for the further consideration of each issue.

I. Moral Justification

"The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature." Nuremberg Code, 1947, Rule 2.

"...It is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity...

"In the field of clinical research a fundamental distinction must be recognized between clinical research in which the aim is essentially therapeutic for a patient, and clinical research the aim of which is purely scientific and without therapeutic value to the person subjected to the research." Declaration of Helsinki, 1964, Preface.

"This review shall determine...whether the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept those risks." Protection of Human Subjects, DHEW, May 30, 1974 (italics added).

In the literature which discusses the ethics of human experimentation surprisingly little attention is devoted to the moral justification of non-therapeutic research. The modern codes which discuss human research, beginning with the Nuremberg Code, simply assume that some studies will be performed "for the sake of the knowledge to be gained" or "for the good of society".

This lack of explicit attention to the problem of moral justification is particularly striking when one considers that the traditional ethic of medicine has been a patient-benefit ethic.³ The obligation primum non nocere has generally

been translated to mean "do nothing which is not intended for the direct benefit of the patient". Because of this tradition patients have generally come to expect what Charles Fried aptly calls "personal care".⁴ Viewed from this perspective, nontherapeutic research is an innovation in the field of medicine and represents a challenge to the traditional ethos of the physician-patient relationship.⁵

The major justification for human research advanced by the few authors who have discussed the issue is a consequentialist argument -- that the social benefits accruing from human experimentation are very great or, conversely, that the harms resulting from the cessation of such research would be extremely grave. Robert Q. Marston, then Director of NIH, presented a cogent case for this point of view in a 1972 lecture at the University of Virginia. He noted, for example, the contrast between Dr. Benjamin Rush, who treated literally hundreds of victims of yellow fever by purging and bleeding, and Dr. Walter Reed, who in a carefully controlled nontherapeutic study demonstrated that yellow fever is transmitted by mosquito bites. Turning to the present, Marston observed that modern medical techniques are significantly more potent, for good or ill, than earlier treatment methods and argued that the only alternative to a plague of iatrogenic illness is the use of controlled clinical trials.⁶ Thus, Marston seems to espouse not only the view that performing nontherapeutic research confers benefits but also the opinion that not performing research causes serious harm. This latter claim may be significant, since human beings are generally thought to have only a weak duty to be beneficent but a much stronger duty not to harm their fellow human beings.⁷

However, even if the good-consequences argument is accepted as being both accurate and important, it is possible that it should be overridden by other

considerations. For example, in the United States in cases involving competent adults, the informed-consent principle functions independently as a procedural check on the performance of all human research. If no adult subjects are willing to consent to participate in a nontherapeutic research project which promises major social benefits, the project will not be carried out. By extension, it can be argued that if no adults in the society were willing to consent to participation in nontherapeutic research, then no nontherapeutic research involving adults would be performed.

If this analysis is correct, it reveals that in the United States nontherapeutic research is considered to be a desirable but not an essential activity. Nontherapeutic research involving adults is able to proceed because subjects can be found who are willing to take part in the research; however, no adult persons are compelled to be research subjects. According to Hans Jonas, this policy is ethically appropriate since progress, even medical progress, is an optional goal and since the duty to participate in nontherapeutic research is not part of the social contract.⁸

One can perhaps conceive of a national health emergency in which a particular society would decide that nontherapeutic research were not merely desirable but essential. In this extreme case, the informed-consent requirement might be waived if no volunteers stepped forward, and the necessary number of subjects would need to be drafted. Similarly, if no researchers were willing to undertake the (possibly dangerous) required research, some researchers would also be conscripted. For less apocalyptic times like the present, however, a combination of consequential and non-consequential considerations seems more appropriate. On the consequential side, the potential benefits of nontherapeutic research are acknowledged to be important for the justification of such

research. On the non-consequential side, the promised benefits of nontherapeutic research are regarded as insufficient to justify the performance of such research unless certain important human rights -- for example, the right of self-determination -- are also respected.

II. Research Design

"The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

"The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment." Nuremberg Code, Rules 3 and 8.

"Clinical research must conform to the moral and scientific principles that justify medical research, and should be based on laboratory and animal experiments or other scientifically established facts.

"Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man." Declaration of Helsinki, Basic Principles 1 and 2.

If, as was argued in the previous section, nontherapeutic research can be morally justified under certain circumstances, then it is possible to consider how such justified research should be designed. The issue of research design can be distinguished only with difficulty from the closely-related issues of risk-benefit analysis and the selection of subjects. Excellent research design helps to minimize risks to subjects, and every design for human research obviously includes a method for selecting subjects. In this section several general issues of research design will be discussed. The succeeding two sections will treat some of the more specific problems associated with risk-benefit analysis and the selection of subjects.

In recent years discussions of ethical issues in human experimentation have tended to focus primary attention on the problem of informed consent. As the quotations from the Nuremberg Code and the Declaration of Helsinki indicate, however, the adequacy of research design has been an important emphasis in codes concerning the ethics of human experimentation. In addition, several recent essays have returned to the discussion of this traditional theme.⁹

A negative principle which several commentators have emphasized is that inadequately designed research should not be performed under any circumstances. In the words of David Rutstein,

It may be accepted as a maxim that a poorly or improperly designed study involving human subjects -- one that could not possibly yield scientific facts (that is, reproducible observations) relevant to the question under study -- is by definition unethical. Moreover, when a study is in itself scientifically invalid, all other ethical considerations become irrelevant. There is no point in obtaining "informed consent" to perform a useless study.¹⁰

According to this view, research which is inadequate scientifically is also inappropriate ethically, since it exposes subjects to risk without a reasonable hope of benefit to anyone.

More positively, adequate research design requires that, whenever possible, laboratory and animal studies should precede the involvement of human subjects in research. The National Commission strongly emphasized this point in its recent deliberations, conclusions, and recommendations concerning fetal research.¹¹ A further principle, as the codes somewhat platitudinously note, is that the investigators involved in any research project should possess the requisite expertise and skills to carry out the research accurately and safely.

Three aspects of research design which have only begun to be debated in the medical-ethics literature of the past fifteen years are randomization,

adaptive design, and the monitoring of double-blind studies. Between 1919 and 1930 R.A. Fisher developed most of the modern concepts of experimental design. These concepts, which were derived from Fisher's agricultural field experiments in England, stressed the importance of performing prospective randomized trials in order to eliminate investigator bias and to achieve maximally-reliable results.¹² In part because of Fisher's influence, the prospective randomized clinical trial has come to be regarded by many as the most authoritative method of hypothesis-testing in biomedical research.

Because the allocation of subjects to medical treatments on a random basis seems to contradict the personal-care ethos of medicine, a lively debate has been carried on concerning alternatives to randomization and the appropriate circumstances for randomization. Alternatives suggested include the judicious use of epidemiological data or the employment of various statistical adjustment methods (e.g., regression and analysis of covariance) to analyze the relative effectiveness of treatments which have been assigned to various patient-subjects solely on clinical grounds.¹³

In discussing appropriate circumstances for randomization, even vigorous advocates of prospective randomized clinical trials, like Thomas Chalmers, concede that a prospective randomized trial should only be undertaken when the relative effectiveness of alternative therapies is unknown.

1. If the clinician knows, or has good reason to believe, that a new therapy (A) is better than another therapy (B), he cannot participate in a comparative trial of Therapy A vs. Therapy B. Ethically the clinician is obligated to give Therapy A to each new patient with a need for one of these therapies.
2. If the physician (or his peers) has genuine doubt as to which therapy is better, he should give each patient an equal chance to receive one or the other therapy. The physician must fully recognize that the new therapy might be worse than the old. Each new patient must have a fair chance of receiving the new and hopefully, better therapy or the limited benefits of the old therapy.¹⁴

For Charles Fried, even this careful formulation is inadequate, since it overlooks the fact that a fully-informed patient might express a clear preference for one of the alternative therapies.¹⁵

Adaptive or sequential design has also been suggested by some commentators as a device for minimizing risks to subjects. The general feature of such designs is that they require periodic assessment of results in a prospective trial and allow for the alteration or termination of the trial on the basis of the information derived from already-completed parts of the trial. Specific designs suggested by Weinstein are the two-stage study, pairwise sequential design, and the employment of an optimal decision rule.¹⁶ In the opinion of Weinstein, "Whether or not randomization is chosen, adaptive methods should be used as a matter of course."¹⁷

Double-blind studies raise unique problems of research design. The plan of such studies requires that the investigator forgo certain types of information so that investigator-bias can be minimized as a factor influencing the results of the studies. In forgoing the knowledge of which treatment is being administered to which subject, the investigator also loses the ability to monitor the effects of the agents or procedures and to recognize when predetermined levels of significance have been reached. These functions should be assumed by a monitoring or safety committee which meets at regular intervals to assess the progress of the study.¹⁸

The general thrust of this section on research design has been to emphasize a single ethical principle -- the minimization of harm to human beings. Thus, if the first section argued that nontherapeutic human research can be morally justified in certain circumstances, this section has added the refinement

that careful, risk-minimizing research design is one necessary condition for ethically-acceptable human experimentation.

III. Risk-Benefit Analysis

"No experiment should be conducted where there is a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

"The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

"During the course of experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe...that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject." Nuremberg Code, Rules 5, 6, and 10.

"Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

"Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others." Declaration of Helsinki, Basic Principles 3 and 4.

"This review shall determine whether...subjects will be placed at risk and, if risk is involved, whether (1) the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks....

"'Subject at risk' means any individual who may be exposed to the possibility of injury, including physical, psychological, or social injury, as a subject in any research, development, or related activity which departs from the application of those established and accepted methods necessary to meet his needs, or increase the ordinary risks of daily life...." Protection of Human Subjects, DHEW, May 30, 1974.

Any proposal for undertaking human research which fails to consider the possible consequences of that research -- including possible harms and benefits¹⁹-- is morally irresponsible. On the other hand, any proposal which does take seriously the benefit-harm calculus is immediately faced with many of the quandaries which have traditionally confronted utilitarian theories of ethics.

Several problems of risk-benefit analysis can be briefly sketched.²⁰ An initial difficulty is ascertaining the various agents who are likely to be subject to risk, e.g., the subject, the subject's family, or society as a whole. A further difficulty is the categorization of various types of risks and benefits, e.g., physical, psychological, or social. When the categories have been established, the identification of specific risks and benefits within each category can proceed, e.g., increased life expectancy or mental depression. The relative probability of occurrence of each potential risk can be projected either in precise percentage-terms or in more general terms, e.g., 75% probability or low probability. In addition, the likely duration of each anticipated risk or benefit can be estimated more or less precisely, e.g., for ten years or for a brief period. A further complexity is the problem of commensurability, whether between agents, categories of risks and benefits, or specific types, probabilities, and durations of risks and benefits. For example, can one legitimately compare a potential risk to an individual subject with a potential benefit to the society as a whole?²¹ Still to be addressed is the difficult issue of collective choice, that is, if several persons undertake risk-benefit analyses and arrive at differing conclusions, can one discover a mechanism for aggregating the results of their individual assessments?²²

To the extent possible, risk-benefit assessments should be made objectively, that is, available statistics on the mortality, morbidity, and other sequelae of particular agents or procedures should be employed. However, it should be recognized that many subjective factors are likely to be involved in any assessment of risks and benefits, and particularly in any attempt to make comparisons among agents or categories of risks and benefits.

Since no mere mortal has access to a master value-table on the basis of which all risks and benefits can be authoritatively assessed and compared, the

most reasonable alternative would seem to be the establishment of a procedure which insures that a variety of competing risk-benefit assessments will be considered and balanced against each other. In particular, it would seem essential to include at some point in the review process the viewpoints of persons, both scientists and non-scientists, who are not institutionally committed to the research enterprise as well as the opinions of persons who are specifically charged with the responsibility of protecting the subjects' interests. From this process of accommodation among divergent viewpoints should emerge a risk-benefit assessment which, even if it is not objective, is at least less one-sidedly subjective than the perspective of any individual participant in the discussion.

What, then, is the role of risk-benefit assessment in determining the appropriateness of human research? Risk-benefit analysis is closely akin to judgments concerning "proportionality" in traditional ethical discussions.²³ It raises the question: Is a proportionate good likely to result if this action is taken? Given the conclusions reached in Section I above concerning the moral justification of nontherapeutic research, it would seem to follow that a favorable (or perhaps a highly-favorable) benefit-risk ratio should constitute a necessary condition for undertaking such research. However, as will be argued in the subsequent section on informed consent, a favorable benefit-risk ratio does not constitute a sufficient condition for proceeding with research. Other conditions must be satisfied as well.

IV. Selection of Subjects

"...The person involved...should be so situated as to be able to exercise free power of choice...and should have sufficient knowledge and comprehension of the subject matter involved as to enable him to

make an understanding and enlightened decision." Nuremberg Code, Rule 1.

"The subject of clinical research should be in such a mental, physical, and legal state as to be able to exercise fully his power of choice." Declaration of Helsinki, Section III, Rule 3b.

"'Informed consent' means the knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice...." Protection of Human Subjects, DHEW, May 30, 1974.

The codes of ethics which discuss human experimentation say very little concerning the selection of subjects. Apart from the short general statements cited above, the codes are silent.

The most extensive systematic discussion of subject selection appears in Hans Jonas' well-known essay "Philosophical Reflections on Human Experimentation". There Jonas proposes "identification" as the principle of recruitment in general. This principle means that initially the recruitment of subjects should take place within the scientific community itself, since the members of that community can most fully identify with the goals and purposes of scientific research. Subsequently, "...one should look for additional subjects where a maximum of identification, understanding, and spontaneity can be expected -- that is, among the most highly motivated, the most highly educated, and the least 'captive' members of the community."²⁴ Negatively, Jonas' principle of identification means that the scientific community ought to refrain from taking advantage of the readiest sources of supply -- "the suggestible, the ignorant, the dependent, and the captive."²⁵

The question of experimentation involving ill subjects presents a special problem for Jonas' position, since some patients may be eager to identify with the goals of biomedical research but at the same time may be quite suggestible and dependent. Jonas argues that the sick should be involved in nontherapeutic

research only as a last resort and then only if the experiment is directly related to their own disease.²⁶

There is in the history of medicine an impressive tradition of auto-experimentation which corresponds closely to Jonas' principle of identification.²⁷ One thinks, for example, of Werner Forssman who performed the first cardiac catheterization on himself, then calmly walked to the radiological department for X-rays with the catheter still in position.²⁸ On the other hand, there is a growing body of evidence to indicate that a substantial fraction of the nontherapeutic research currently being conducted in the United States involves precisely those persons who, according to the principle of identification, are the least eligible candidates for such research. Specifically, clinic or ward patients and prisoners seem to be involved to a disproportionate extent as the subjects of nontherapeutic research.²⁹ In some nontherapeutic research projects at urban medical centers, seventy to ninety per cent of the subjects are ward patients. One sociological survey also indicates that qualitative discrimination may accompany this quantitative overrepresentation. In a study of 352 research projects, Bernard Barber and associates found that ward or clinic patients were much more likely to be involved in research with an unfavorable risk-benefit ratio than were their private-patient counterparts.³⁰

There are, of course, historical reasons for the location of many major medical centers in areas of urban poverty. The design of some research projects also requires stable or quarantined populations like those available in various closed institutions. However, these excusing conditions should not deflect attention from the fact that in contemporary American society the risks and benefits of nontherapeutic research are inequitably distributed. Even if Jonas' stringent standard of noblesse oblige cannot be reached, simple justice would

seem to require that each economic class and group bear a proportionate share of research risks. Given the marginal nature of the sacrifices required in most nontherapeutic research, adequate numbers of subjects from each class and group may be willing to volunteer. Affirmative action programs which seek to involve more well-educated and well-to-do persons may also be successful. If not, then the public will in effect have voted to assign a higher priority to other types of civic activity.³¹

Equity in the selection of subjects (and its obverse, non-discrimination against the sick, the prisoner, and the less fortunate) thus constitutes an additional standard for nontherapeutic research. Like adequate research design and a favorable benefit-risk ratio, it is a necessary but not a sufficient condition for ethically-acceptable research.

V. Informed Consent

"The voluntary consent of the human subject is absolutely essential.

"This means that the person involved should have the legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the methods and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment....

"During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible." Nuremberg Code, Rules 1 and 9.

"The nature, the purpose, and the risk of clinical research must be explained to the subject by the doctor.

"Clinical research on a human being cannot be undertaken without his free consent, after he has been fully informed; if he is legally incompetent, the consent of the legal guardian should be procured.

"The subject of clinical research should be in such a mental, physical, and legal state as to be able to exercise fully his power of choice.

"Consent should as a rule be obtained in writing....

"At any time during the course of clinical research the subject or his guardian should be free to withdraw permission for research to be continued." Declaration of Helsinki, Section III, Rules 2, 3a, 3b, 3c, and 4b.

"'Informed consent' means the knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion. The basic elements of information necessary to such consent include:

- (1) A fair explanation of the procedures to be followed, and their purposes, including identification of any procedures which are experimental;
- (2) a description of any attendant discomfort and risks reasonably to be expected;
- (3) a description of any benefits reasonably to be expected;
- (4) a disclosure of any appropriate alternative procedures that might be advantageous for the subject;
- (5) an offer to answer any inquiries concerning the procedures; and
- (6) an instruction that the person is free to withdraw his consent and to discontinue participation in the project or activity at any time without prejudice to the subject." Protection of Human Subjects, DHEW, May 30, 1974.

Since Nuremberg no aspect of human experimentation has received greater attention than the issue of informed consent. As the foregoing quotations suggest, during the past thirty years the language employed to describe informed consent has gradually been refined and made more precise.

Several commentators have noted that informed consent can be analyzed into two component parts. The information-component refers to a reasonable disclosure by the investigator and adequate comprehension by the prospective subject. The consent aspect of informed consent refers to an uncoerced decision by which the subject agrees to take part in the disclosed and comprehended procedure or project.

A variety of justifications or rationales for the informed-consent requirement have been proffered. According to Paul Ramsey, "The principle of an informed consent is the cardinal canon of loyalty joining men together in medical practice and investigation."³³ Within the American legal tradition of the twentieth century, major emphasis has been placed on protecting the right of self-determination and the bodily integrity of patients (and, by implication, of patient-subjects). Court decisions reflecting this emphasis include Schloendorff v. New York Hospital, decided in 1914, and three 1972 decisions, Cobb v. Grant, Wilkinson v. Vesey, and Canterbury v. Spence.³⁴ Other rationales for the informed-consent principle are suggested by Alexander Capron: "to avoid fraud and duress," "to encourage self-scrutiny by the physician-investigator," "to foster rational decision-making," and "to involve the public."³⁵ Thus, both consequentialist and non-consequentialist justifications for informed consent have been advanced, with the latter predominating both in the relevant court decisions and in the secondary literature.

Despite the impressive consensus concerning the significance and necessity of the informed-consent principle, several specific topics continue to spark vigorous debate. Three of these topics will be briefly noted: (1) additional types of information which should be conveyed to subjects; (2) subjective vs. objective standards for informed consent; and (3) exceptions to the informed-consent requirements.³⁶ Proponents of fuller disclosure to potential research subjects have advocated that information concerning the following questions should be provided to each subject prior to his or her enlistment in any nontherapeutic research project: the use of randomization in the study³⁷; the existence of a placebo group³⁸; measures which will be taken to insure the early detection and minimization of harms to subjects³⁹; and provisions

for the correction of, or compensation for, research-related injuries.⁴⁰ In addition, one commentator has proposed that during the course of a clinical trial already-enlisted subjects should be informed of any findings of the study which might affect their decisions to remain in, or to withdraw from, that study.⁴¹

The nature of the standards for informed consent seems to have been left somewhat unclear by the three major informed-consent court decisions of 1972. All three decisions agreed that a patient-oriented standard ought to be preferred to the traditional "reasonable medical practice" standard. However, two of the decisions seem to require that a physician (or physician-investigator) disclose all material facts which a reasonable person would wish to know.⁴² The California court, on the other hand, adopted a more subjective standard, arguing that "The scope of the physician's communications to the patient...must be measured by the patient's need, and that need is whatever information is material to the decision."⁴³ In the research context the choice of a reasonable-patient or a subject's-need standard will significantly affect the stringency of the disclosure requirement.

Several commentators have also raised the question whether the informed-consent requirement can be waived in any nontherapeutic research situations. The Kefauver-Harris amendments to the Federal Food, Drug and Cosmetic Act in 1962 seemed to allow for such an exception by requiring investigators to obtain the consent of the subject or the subject's representative "except where they deem it not feasible or, in their best professional judgment, contrary to the best interests of such human beings."⁴⁴ However, the regulations implementing this provision seem clearly to confine this exception to the situation in which an unlicensed drug is administered to a patient solely for therapeutic reasons.⁴⁵

Robert Levine suggests that the purpose of some studies may need to remain undisclosed if the goals of the study are to be accomplished; however, he argues that in such cases the prospective subjects should be informed that some information is being withheld from them until the conclusion of their participation.⁴⁶ Perhaps certain types of unseen-observer research are the strongest candidates for exception from the informed-consent requirement.⁴⁷ Even in these cases, however, unconsented nontherapeutic research -- while perhaps posing no direct risks to the unknowing subjects -- may constitute a violation of their right of privacy.⁴⁸

The issue of informed consent is thus a central topic in discussions concerning the ethics of human experimentation. As noted previously in the section on research design, informed consent alone is insufficient to justify proceeding with research, particularly in cases where no useful purpose can be served by an experiment. However, reasonably free and adequately informed consent is clearly one of the necessary conditions for ethically-acceptable human research.

IV. Social Control

"Safeguarding the rights and welfare of subjects at risk in activities supported under grants and contracts from DHEW is primarily the responsibility of the institution which receives or is accountable to DHEW for the funds awarded.... In order to provide for the adequate discharge of this organizational responsibility, it is the policy of DHEW that no activity involving human subjects to be supported by DHEW grants or contracts shall be undertaken unless a committee of the organization [an Institutional Review Board]⁴⁹ has reviewed and approved such activity, and the institution has submitted to DHEW a certification of such review and approval, in accordance with the requirements of this part." Protection of Human Subjects, DHEW, May 30, 1974.

The issue of social control differs significantly from the issues discussed

in Sections II-V above. From an ethical perspective, it seems to raise procedural rather than substantive questions.

Within the professions generally and within the medical profession in particular the preferred method of social control has been self-regulation.⁵⁰ In the context of clinical practice, where the physician's exclusive concern was to benefit the patient, a system which relied heavily on professional self-regulation may have proved sufficient to protect the best interests of the professional's clients.⁵¹ In the nontherapeutic research context, however, the welfare of the subject ceases, by definition, to be the (medical or non-medical) professional's exclusive concern.

In the United States the primary mechanism for the social control of publicly-supported human research has been peer review of proposed research projects by expert scientists and clinicians. These expert reviewers have fulfilled a significant role, particularly in the assessment of research design and risk-benefit ratios. Within the highly-developed NIH review mechanism, the peer-review findings of the study sections have been complemented by the judgments of the Division of Research Grants and the Advisory Councils.⁵²

During the decade of the 1960's an additional mechanism for the control of human research was developed. Early in the decade, and even during the late 1950's, local peer review committees began to be established, at first in a small minority of medical centers. Later, when the Public Health Service began to require prior review as a condition for grant support, the number of such local committees multiplied rapidly. By the end of 1969 local peer review committees were, in the words of Bernard Barber, "probably universally established in biomedical research institutions."⁵³

During the 1970's numerous proposals have been advanced for improving the

quality of social control in the field of human experimentation. Some of these proposals have suggested changes in the structure and/or functions of local review committees, or Institutional Review Boards, as they are now officially called. For example, some commentators have urged -- and FDA regulations require -- that the membership of Institutional Review Boards be broadened to include lay and non-scientific points of view.⁵⁴ Additional responsibilities have also been proposed for Institutional Review Boards, including the monitoring of subject selection and the consent process and on-site evaluation of studies in progress.⁵⁵ Several new modes and mechanisms of social control are intended to supplement the role of local Institutional Review Boards and other existing review bodies. The National Commission for the Protection of Human Subjects has been charged with multiple tasks, including the development of national guidelines for the conduct of biomedical and behavioral research. The Commission will also investigate whether subjects are adequately protected in research contexts where current DHEW guidelines do not apply.⁵⁶ Building on the foundation laid by the Commission, soon-to-be-created Ethical Advisory Boards will complement the efforts of Institutional Review Boards and other review bodies by providing national review for particular categories of research and by seeking to apply generally-accepted ethical standards to complex individual cases.⁵⁷

As noted above, social control is a procedural rather than a substantive issue. Therefore it is not in itself one of the necessary conditions for ethically-acceptable human research. Rather, it is a means for ensuring, insofar as possible, that research is conducted in accordance with basic ethical principles. Thus, from an ethical perspective the primary criterion for judging the adequacy of any particular social-control mechanism will be the

extent to which that mechanism promotes values like those identified in earlier sections of this essay.

VII. Compensation of Injured Research Subjects

Even if a research project is exemplary in its design, risk-benefit ratio, selection of subjects, and provision for informed consent, and even if the project has been thoroughly reviewed and carefully monitored from inception to implementation -- it is possible that a participant in the project will suffer injury. It is also possible, and indeed likely in a situation like the one described, that the injury will have been due to no fault of the investigator. Let us suppose, hypothetically, that such an unanticipated and seemingly-unavoidable injury has occurred and, further, that it has been suffered by a normal volunteer for whom the study in question was totally nontherapeutic. What debt, if any, does society owe to the injured subject?

The major codes of ethics are totally silent on the subject of compensation for research-related injuries. However, there is a significant and expanding secondary literature which discusses the issue; most commentators have advocated some form of compensation for injured subjects.⁵⁸ In addition, an inter-agency DHEW task force, the Secretary's Task Force on the Compensation of Injured Research Subjects, is currently completing an intensive study of this question.⁵⁹

In the initial section of this essay it was argued that, except in cases of national emergency, no citizen should be required to take part in non-therapeutic research. It would be possible to conclude that since society does not mandate any subject's participation, neither does it bear responsibility

for the untoward effects of any individual's free decision. On the other hand, however, the society requires that certain types of nontherapeutic research be done, e.g., Phase I testing of most new drugs on normal volunteers. In addition, the society supports many kinds of nontherapeutic research projects which cannot be carried out unless substantial numbers of persons volunteer to participate. Moreover, it can be argued that the freedom of the individual's choice is a less significant consideration than the fact of the individual's having been injured while contributing to the social good. In the context of military service, society compensates both draftees and volunteers who suffer service-connected disabilities. In an analogous way, the principle of justice would seem to require compensation for casualties of the war on disease, without regard to their volunteer status.

Even if arguments based on compensatory justice are rejected, the probable implications of an expanded concept of informed consent may lead to a similar conclusion. As noted above in Section V, some commentators have urged that prospective subjects of nontherapeutic research be advised concerning provisions for the repair of, or compensation for, research-related injuries. If this type of information is in fact imparted to potential subjects, -- as it should be, in the author's view -- then it is likely that increasing numbers of subjects will request guarantees of restorative medical care or, in cases where restoration is impossible, assurance of equitable compensation for injuries.

Efforts to develop a mechanism for the equitable compensation of injured research subjects will undoubtedly be confronted with numerous administrative difficulties. The clearcut case of a no-fault injury suffered in the course of totally-nontherapeutic research will be relatively straightforward in

terms of causation and presents a strong claim for compensation. Less clear in both respects will be cases in which ill patient-subjects seem to suffer injury while participating in mixed research (e.g., research in which the therapeutic/nontherapeutic ratio is 60/40).⁶⁰ In addition, for both simple and complex cases an appropriate institutional framework will need to be created and a calculus for determining appropriate levels of compensation will need to be found.

Unlike the ethical principles developed in Sections II-V above, the principle of equitable compensation for research-related injuries is a contingent principle, which can only be applied in cases where actual injury occurs. Thus, the requirement of equitable compensation can be categorized as a subsidiary ethical principle and should be regarded as a necessary condition for ethically-acceptable nontherapeutic research in cases where subjects of that research suffer injury.

Conclusion

In the Summa theologiae of Thomas Aquinas there appears a question entitled simply "On War." Thomas begins his discussion of that question by asking, "Is it always wrong to wage war?" He answers in the negative but adds that in order for a war to be just, i.e., morally right, "three things are required": the authority of the prince, a just cause, and a right intention on the part of those waging the war. Thomas apparently considered all three of these criteria to be essential, for in discussing "right intention" he noted:

It may happen that even if a war is declared by the authority of the prince and even if the cause is just,

the war may nevertheless be rendered illicit because of a wrong intention.⁶¹

The formal structure of the present essay closely parallels Thomas' question on war. Section I raised the issue whether nontherapeutic research can be morally justified under any circumstances and concluded that such justification is in principle possible. Sections II through V identified four general requirements for ethically-acceptable nontherapeutic research: adequate research design; a favorable risk-benefit ratio; equitable selection of subjects; and reasonably free and adequately informed consent by the subjects. In Section VI it was argued that social control is a procedural value which should assist in the implementation of the four general requirements. And in Section VII the subsidiary principle of equitable compensation for research-related injuries was identified.

No attempt has been made to explore the relative importance of the four general requirements discussed in Sections II through V. However, the language of conditionality has been employed to assert the essential significance of each. It is the thesis of this essay that the four general requirements -- adequate research design, favorable risk-benefit ratio, equitable subject selection, and informed consent -- are individually necessary and jointly sufficient to provide moral justification for any proposed nontherapeutic human research.

FOOTNOTES

¹This definition is adapted from a definition suggested by Robert J. Levine in his essay for the Commission entitled "The Boundaries Between Biomedical or Behavioral Research and the Accepted and Routine Practice of Medicine," unpublished paper, 14 July 1975.

²The definitions of therapeutic and nontherapeutic research closely follow definitions proposed by Charles Fried (Medical Experimentation: Personal Integrity and Social Choice [New York: American Elsevier, 1974], pp. 25-26. The language of design is preferred to the language of intention since it is more objective and less likely to become entangled with the problem of self-deception.

³Robert M. Veatch, "Ethical Principles in Medical Experimentation," in Alice M. Rivlin and P. Michael Timpane, eds., Ethical and Legal Issues of Social Experimentation (Washington: Brookings Institution, 1975), pp. 24-26.

⁴Fried, Medical Experimentation, pp. 47-60

⁵Because of this apparent conflict in the physician-investigator's roles, one physician has recently proposed that the two roles be rigorously separated. See Howard M. Spiro, "Constraint and Consent -- On Being a Patient and a Subject," New England Journal of Medicine 293(22): 1134-1135, 27 November 1975.

⁶Robert Q. Marston, "Medical Science, the Clinical Trial, and Society," address delivered at the University of Virginia, Charlottesville, Va., November 10, 1972.

⁷William K. Frankena, Ethics (2nd ed.; Englewood Cliffs, N.J.: Prentice-Hall, 1973), pp. 45-48. It is, of course, a further question whether allowing harm to occur to a person is morally equivalent to causing harm to that person.

⁸Hans Jonas, "Philosophical Reflections on Human Experimentation," in Paul A. Freund, ed., Experimentation with Human Subjects (New York: George Braziller, 1970), pp. 6-15.

⁹David D. Rutstein, "The Ethical Design of Human Experiments," in Freund, ed., Experimentation with Human Subjects, pp. 383-401; Fried, Medical Experimentation, passim; Milton C. Weinstein, "Allocation of Subjects in Medical Experiments," New England Journal of Medicine 291(24): 1278-1285, 12 December 1974; William W. May, "The Composition and Function of Ethical Committees," Journal of Medical Ethics 1(1): 23-29, April 1975.

¹⁰Rutstein, "The Ethical Design of Human Experiments," p. 384.

¹¹Office of the Secretary, DHEW, "Protection of Human Subjects: Fetuses, Pregnant Women, and In Vitro Fertilization," Federal Register 40(154): 33545, 33547-33548, 8 August 1975.

¹²William G. Cochran, "Experimental Design: I. The Design of Experiments," International Encyclopedia of the Social Sciences, Vol. 5, p. 246. See also Ronald A. Fisher, The Design of Experiments (7th ed.; New York: Hafner, 1960).

¹³Weinstein, "Allocation of subjects in Medical Experiments," pp. 1279-1281; Fried, Medical Experimentation, p. 159. See also Donald J. Campbell, "Experimental Design: III. Quasi-Experimental Design," International Encyclopedia of the Social Sciences, Vol. 14, pp. 259-263.

¹⁴Lawrence W. Shaw and Thomas C. Chalmers, "Ethics in Cooperative Clinical Trials," Annals of the New York Academy of Sciences 169(Art. 2): 487-488, 21 January 1970.

¹⁵Fried, Medical Experimentation, pp. 153-154.

¹⁶Weinstein, "Allocation of Subjects in Medical Experiments," pp. 1281-1284. See also P. Armitage, "Sequential Analysis," International Encyclopedia of the Social Sciences, Vol. 14, pp. 187-192.

¹⁷Weinstein, ibid., p. 1284

¹⁸On this issue see Fried, Medical Experimentation, p. 148

¹⁹In this section the term "risk(s)" and "harm(s)" are used interchangeably, and the concepts "risk (of harm)" and "(probability of) benefit" are considered to be symmetrical.

²⁰Some of these problems have been more thoroughly explored in an excellent paper prepared for the Commission by Robert J. Levine ("The Role of the Assessment of Risk-Benefit Criteria in the Determination of the Appropriateness of Research Involving Human Subjects," unpublished paper, 27 October 1975).

²¹For a brief discussion of several problems inherent in cost-benefit analysis see Fried, Medical Experimentation, pp. 81-87. See also Nicholas Georgescu-Roegen, "Utility," International Encyclopedia of the Social Sciences, Vol. 16, pp. 236-267.

²²The problem of collective choice has been vigorously debated by welfare economists. For a recent survey of the various positions in this debate which includes non-technical discussion and a comprehensive bibliography see Amartya K. Sen, Collective Choice and Social Welfare (San Francisco: Holden-Day, 1970).

²³The Declaration of Helsinki employs the language of proportionality in its third Basic Principle.

²⁴Jonas, "Philosophical Reflections on Human Experimentation," p. 18.

²⁵Ibid., p. 20.

²⁶Ibid., pp. 21-24.

²⁷Lawrence K. Altman, "Auto-Experimentation: An Unappreciated Tradition in Medical Science," New England Journal of Medicine 286(7): 346-352, 17 February 1972; Fried, Medical Experimentation, pp. 167-168.

²⁸A.J. Benatt, "Cardiac Catheterization;" reprinted in Jay Katz, with the assistance of Alexander Morgan Capron and Eleanor Swift Glass, Experimentation with Human Beings (New York: Russell Sage Foundation, 1972), p. 138.

²⁹Bernard Barber, et al., Research on Human Subjects; Problems of Social Control in Medical Experimentation (New York: Russell Sage Foundation, 1973), pp. 53-57; Katz, Experimentation with Human Beings, pp. 342-345, 633-634, 740-746; Bradford H. Gray, Human Subjects in Medical Experimentation, pp. 241-243; Fried, Medical Experimentation, pp. 165-171; Henry Foster, Jay Katz, and Franz Ingelfinger, "The Poor," in Experiments and Research with Humans: Values in Conflict (Washington: National Academy of Sciences, 1975), pp. 150-160.

³⁰Barber, et al., Research on Human Subjects, pp. 54-56.

³¹Fried, Medical Experimentation, pp. 169-170.

³²Paul Ramsey, The Patient as Person: Explorations in Medical Ethics (New Haven, Yale University Press, 1970), pp. 1-11; Jon R. Waltz and Thomas W. Scheuneman, "Informed Consent to Therapy," reprinted in Katz, Experimentation with Human Beings, pp. 579-581; Alexander M. Capron, "Informed Consent in Catastrophic Disease Research and Treatment," University of Pennsylvania Law Review 123(2): 413-414, December 1974.

³³Ramsey, ibid., p. 5.

³⁴An excerpt from the Schloendorff v. New York Hospital decision is reprinted in Katz, Experimentation with Human Beings, p. 526. The sources for the three 1972 decisions, respectively, are 502 P.3d 1 (1972), 295 A.2d 676 (1972), and 464 F.2d 772 (D.C. Cir.). For a thorough discussion of these latter three cases see Capron, "Informed Consent in Catastrophic Disease Research and Treatment," pp. 403-423.

³⁵Capron, ibid., pp. 364-376.

³⁶The topics of proxy consent and substituted judgment are also highly significant but are too complex to be analyzed satisfactorily in a survey essay. For an excellent introduction to some of the ethical issues involved in the analysis of these two topics, Richard A. McCormick, "Proxy Consent in the Experimentation Situation," Perspectives in Biology and Medicine 18(1): 2-20, Autumn 1974.

³⁷Franz J. Ingelfinger, "The Poor," in Experiments and Research with Human Subjects, p. 169; Fried, Medical Experimentation, pp. 33-34.

³⁸Food and Drug Administration regulations stipulate that every subject must be "provided with a fair explanation of pertinent information concerning the investigational drug, and/or his possible use as a control" (Code of Federal Regulations 21, 130.37 [1971]). See also Veatch, "Ethical Principles in Medical Experimentation," pp. 52-53.

³⁹Robert J. Levine, "The Nature and Definition of Informed Consent in Various Research Settings," unpublished paper prepared for the National Commission, December 1975, p. 16.

⁴⁰Ibid.; Veatch, "Ethical Principles in Medical Experimentation," pp. 53-54.

⁴¹Fried, Medical Experimentation, pp. 35-36. Fried's proposal illustrates the fact that as a randomized comparison of two therapies approaches the predetermined level of significance, the subjects assigned to the less desirable therapy gradually approach the situation of normal volunteers in a totally-nontherapeutic study.

⁴²Capron, "Informed Consent in Catastrophic Disease Research and Treatment," pp. 406-408.

⁴³502 P.2d at 11; cited by Capron, ibid., p. 406.

⁴⁴U.S. Code 21, 355 (1972).

⁴⁵Code of Federal Regulations 21, 130.37(b) and (f) (1971). See also Fried, Medical Experimentation, pp. 39-41.

⁴⁶Levine, "The Nature and Definition of Informed Consent," pp. 30-31.

⁴⁷Levine argues for the possible moral justifiability of unseen-observer research without specifying whether such research would be therapeutic or nontherapeutic in its design (ibid., p. 78).

⁴⁸Veatch, "Ethical Principles in Medical Experimentation," p. 49.

⁴⁹The words in brackets were substituted for "a committee of the organization" in Technical Amendments to the May 30, 1974, guidelines which were published in Federal Register 40(50): 11854-11558, 13 March 1975.

⁵⁰Gray, Human Subjects in Medical Experimentation, pp. 245-246; Barber, et al., Research on Human Subjects, pp. 173-174.

⁵¹This judgment itself is a matter of considerable debate. See, for example, Eliot Freidson, The Profession of Medicine (New York: Dodd, Mead, 1970), chap. 7.

⁵²William J. Curran, "Government Regulation of the Use of Human Subjects in Medical Research: The Approach of Two Federal Agencies," in Freund, ed., Experimentation with Human Subjects, pp. 430-433.

⁵³Barber, Research on Human Subjects, p. 148.

⁵⁴Code of Federal Regulations 21, 130.3 (1971); first published in Federal Register 32:8753, 20 June 1967. See also Veatch, "Ethical Principles in Medical Experimentation," pp. 38-41.

⁵⁵Office of the Secretary, DHEW, "Protection of Human Subjects: Fetuses, Pregnant Women, and In Vitro Fertilization," p. 33529 (Code of Federal Regulations 45, 46.205(2)(2) [1975]).

⁵⁶Public Law 93-348, Section 202, U.S. Statutes at Large 88: 349-350.

⁵⁷Office of the Secretary, DHEW, "Protection of Human Subjects: Fetuses, Pregnant Women, and In Vitro Fertilization," pp. 33526, 33529.

⁵⁸Fried, Medical Experimentation, pp. 26-28, 171-172; Clark C. Havighurst, "Compensating Persons Injured in Human Experimentation," Science 169: 153-157, 10 July 1970; Irving Ladimer, "Clinical Research Insurance," Journal of Chronic Disease 16: 1229-1235, 11 December 1963; Note, "Medical Experiment Insurance," Columbia Law Review 70(5): 965-979, May 1970; Edwin Roth and Paul Rothstein, "Non-Fault-Based Medical Injury Compensation Systems," in the Appendix to the Report of the Secretary's Commission on Medical Malpractice (Washington DHEW, 1973). pp. 450-493.

⁵⁹Personal communication from Dr. Charles R. McCarthy, Division of Legislative Analysis, Office of the Director, NIH.

⁶⁰The question of compensating subjects injured in the course of mixed research will be simplified if a general system of compensation for medical accidents is established. On this point see Clark C. Havighurst and Laurence R. Tancredi, "'Medical Adversity Insurance' -- a No-Fault Approach to Medical Malpractice and Quality Assurance," Milbank Memorial Fund Quarterly 51(2): 125-168, Spring 1973.

⁶¹Summa theologiae 2-2, question 40, article 1.

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