MASTER

INSTRUMENTATION FOR MEDICAL DIAGNOSIS AND RESEARCH
WITH RADIONUCLIDES IN THE DEVELOPING COUNTRIES

Progress Report
for period 1 June 1977 - 31 May 1978

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A B S T R A C T

This project seeks to bring about a more effective use of nuclear instruments in medical applications of radionuclides in developing countries by facilitating selection of appropriate applications, by stimulating the design of instruments capable of performing these applications satisfactorily under the conditions prevailing, and by encouraging improved maintenance. A pilot cost-effectiveness analysis of nuclear medicine applications has been completed, suggesting two topics for further investigation and demonstrating that such analyses can yield useful insights. In the realm of instrument design, we have further developed our prototype well scintillation counter, provided three such instruments for tests in the field, and encouraged its production by others. In addition, we have examined design issues for liquid scintillation counters, radiorespirometry counting devices, whole-body counters, and electrical power supplies. We have completed a survey of maintenance in 8 countries in Southeast Asia, and are analyzing the results. Preparations are underway for surveys in three further regions.

PROGRESS REPORT

I. Introduction

Contract No. E(11-1)-2742 (currently EY-76-C-02-2742.A001) was established by ERDA with the IAEA, effective 1 June 1975 for a period of 2 years, and renewed effective 1 June 1977 for a further period of 1 year, to study "Instrumentation for Medical Diagnosis and Research with Radionuclides in the Developing Countries." The investigation had its genesis in a recommendation by the USAEC at the IAEA's 1974 General Conference that the IAEA, with U.S. support, seek to assure a more effective use of nuclear instrumentation in medical applications of radionuclides in developing countries. Subsequently, ERDA made available to this project at the IAEA for a period of 2 years, starting 1 November 1976, a cost-free expert in the person of Mr. A.C. Morris, an electronics engineer from Oak Ridge National Laboratory.

The project was foreseen to have 3 primary facets: (1) the identification of those diagnostic applications or research areas in which radionuclides could make the most important contribution to health, (2) the determination of what instruments are required, and the respective performance characteristics they should have, to carry out the identified investigations, and (3) the development of improved strategies to maintain the instruments while in use. Progress has been made during the current year in all 3 areas, as summarized below.

II. Radionuclide Applications

A. Current applications in Southeast Asia

A survey has been conducted in Southeast Asia, primarily to assess the state of maintenance of nuclear medicine instrumentation as discussed later. However, supplementary data were collected to characterize current nuclear medicine applications in the region.

The survey encompassed 8 countries: Bangladesh, India, Malaysia, Pakistan, Philippines, Singapore, Sri Lanka, and Thailand. With the assistance of a "national coordinator" in each country an attempt was made to collect information from every currently functioning nuclear medicine unit. Coverage of laboratories using radionuclides in primarily biochemical applications or in basic research was not sought. While inevitably some units were omitted, and not all data are completely accurate, the resultant picture is undoubtedly more informative than what has heretofore been available.

A preliminary listing of the nuclear medicine applications in 54 nuclear medicine units in 7 of these countries (omitting India, for which the data are not yet collated) is given in Table 1. These applications tend to be similar to those made in developed countries, although studies distinctive to gamma cameras (e.g. imaging of dynamic processes) are inevitably under-represented. Except for the special case of a survey of urinary morphine in troops in one country, studies of the endocrine system (overwhelmingly thyroid) dominate. As to measurement procedure, 3 are paramount: (1) probe measurements of ^{131}I uptake by the thyroid, (2) imaging (mainly rectilinear scanning) of thyroid, liver, and brain, and (3) in-vitro assays using well scintillation counters and ^{125}I .

B. Cost-effectiveness analysis of nuclear medicine applications in developing countries

The activities under this topic have centered upon a research project conducted under contract with the Agency by Prof. S.J. Adelstein (Harvard Medical School) and colleagues, and a consultants' meeting held in May 1978 to review their findings and to consider in what direction such investigations might profitably be taken in the future. The initial objectives were to identify certain nuclear medicine applications of possible special relevance in developing countries, and by means of cost-effectiveness analyses to appraise both the potential of these applications and the feasibility of carrying out such cost-effectiveness analyses of them.

1. Research contract with Harvard Medical School

Four nuclear medicine applications were examined by Prof. Adelstein's group, in varying depth. They were given specific form by relating them to the conditions found in India. They are illustrated by a draft analysis of the

hepatitis B application (Attachment 1), which has been examined in greater detail than the other applications. This draft represents work by both the Harvard group and Agency staff members.

To summarize the 4 studies very briefly:

(1) Radiometric determination of mycobacterial growth

The objective was to determine whether radiorespirometry (measurement of $^{14}\text{CO}_2$ evolved by bacteria from a culture medium incorporating a ^{14}C -labeled substrate) could contribute usefully to the detection of pulmonary TB cases or to the testing of the sensitivity of the TB organisms to various drugs. The conclusions were pessimistic on the primary grounds that culturing the TB organisms under conditions appropriate for radiorespirometry has proved peculiarly difficult. However, the technique looked potentially cost-effective for hospitalized patients if these problems could be solved: its greater speed could substantially reduce patient length-of-stay and therefore costs in hospitals.

(2) Radioimmunoassay of hepatitis B surface antigen (HBsAg)

The objective was to determine whether use of this procedure for screening out blood donors carrying hepatitis B surface antigen would be cost-effective in developing countries. The analysis fairly clearly identified which few of the many parameters involved were of greatest importance in deciding the issue, namely the cost consequences of causing hepatitis B by blood transfusion, costs of alternative screening tests, and the prevalence of hepatitis B among potential donors (see Attachment 1). The values of these parameters are not now well enough known to allow clear answers, but they can certainly be made more precise by collection of further data.

(3) Radiobromide partition test for diagnosing tubercular meningitis

The objective was to determine whether this radioisotope test (partition of $^{82}\text{Br}^-$ between plasma and CSF) would be cost effective in distinguishing tubercular

meningitis from other forms of meningitis. The analysis was partly compromised by growing suspicions that the true positive and false positive rates of the new test (i.e., new to most Indian hospitals) might be less favorable than originally believed. The results showed the complex interplay of prevalence rates, and of cure rates attributable to alternative therapies, upon the estimates of benefits of a proposed new test. If the test performance warranted it, better data could be collected on these points in selected communities.

(4) Radioassays for thyroid hormones in population screening

The objective was to assess the costs and reliability of alternative radioassay procedures in screening certain population groups for thyroid disorders, in particular hypo- and hyperthyroidism in iodine-sufficient and iodine-deficient areas. The study drew attention to the scantiness of data, but concluded (1) that attention should first be focussed on hypothyroidism in iodine-deficient areas, (2) that radioassay tests based on a drop of blood absorbed on filter paper show special promise for the conditions found in many developing countries, and (3) that, in general, radioassay for thyroid disease is a promising area of expansion for nuclear medicine in developing countries.

The 4 foregoing examples of nuclear medicine applications in developing countries were not selected chiefly on the basis of a belief that they would be the most important, but rather using a variety of additional criteria such as possible availability of data and diversity of medical field. Nevertheless, the predominance of in-vitro procedures does reflect the investigators' feeling that such procedures may tend to prevail, from a cost-effectiveness viewpoint, over in-vivo procedures.

2. Consultants' meeting: Medical applications of radionuclides in developing countries - cost-effectiveness analysis

This meeting, whose first task was to review the findings of the Harvard group, was attended by (in addition to the Harvard group) 3 Indians experienced in the fields examined and two other specialists in certain of the topics. Some amplification of the data base for the foregoing studies was possible, and useful insights were provided about conditions obtaining in developing countries.

Several suggestions arose with regard to continuation of these studies. Of the 4 test cases examined by the Harvard group, 2 seemed ripe for further analysis in particular developing country settings, namely detection of hepatitis B surface antigen and assay of thyroid hormones. For hepatitis B the important parameters, especially prevalence and various costs, should be quantified more accurately, and the costs should be compared with those attending alternative screening techniques. For assay of thyroid hormones, two types of investigation might be envisaged: (a) testing of procedures for screening hypothyroids in selected iodine deficient areas, including methodological issues such as practicality and reliability of the filter-paper technique, and (b) evaluation of strategies for diagnosing thyroid status efficiently by radioimmunoassay, in particular sequencing these assays in such a manner as to reduce the number of tests required for each patient. It was also felt that radioimmunoassays (or related in-vitro procedures) and radiorespirometry were promising techniques to explore in relation to infectious diseases and drug resistance, although cost-effectiveness analysis would be premature until technical feasibility of the procedures was assured in certain applications.

In general, while the participants recognized the complexity of cost-effectiveness analysis and the ambiguities associated with inadequacies in the data base, there was a consensus that rational evaluation of potential nuclear medicine applications in developing countries should nevertheless be rewarding.

III. Design of Instruments

A. Instruments currently deployed in Southeast Asia

In considering what sorts of instruments are required for nuclear medicine in developing countries, it is instructive to see what instruments are currently in use. The next to last column of Table 2 is a nearly complete list of instruments now deployed in 51 laboratories of the 7 Southeast Asia countries (excluding India) covered in the recent survey (see above).

B. Well scintillation counters

Well scintillation counters are one of the most basic and most common nuclear medicine instruments; we have therefore studied these instruments first with regard

to design attributes and possible innovations that would be advantageous in developing countries.

1. Commercially available instruments

We have collected data on commercially available well scintillation counters, valid as of about 1 January 1978, as shown in Attachment 2.

2. Consultants' meeting on design requirements

In late May, 1977, a consultants' meeting was held in Vienna to review design requirements for well scintillation counters in the context of this contract. Their report is embodied in Attachment 3 (which also contains an earlier version of the data on commercial well scintillation counters of Attachment 2).

In summary, the consultants agreed that ideally a laboratory should start with a manual counter, and upgrade it for automatic operation only when justified either by the number of samples or the length of counting time. Defects arising in the automatic features should not preclude continued manual operation. In view of the frequency of power failures, the possibility of operating from rechargeable batteries should exist. Spare parts and maintenance should be indigenously available to the maximum extent possible. Currently available commercial well scintillation counters do not exhibit many of these characteristics.

3. Agency's prototype counter

As described in our progress report last year, we have constructed a prototype counter that offers many of the features favored by the consultants. Its status as of October 1977 is summarized in Attachment 4. Since then, further tests have confirmed the mechanical robustness and reliability of the system, and the calculator programs have been given greater capability and made easier to use. In present form the programs in fact offer substantially more rigorous quality control possibilities than do most commercial instruments, including those that incorporate mini-computers. Four prototypes have been built; one is undergoing tests in our laboratory and another in a London laboratory,

while the other two have just been shipped to Khartoum and Agra, respectively, for use in research contract projects. In summary, our experience with these devices fully confirms our hopes that in simplicity, in ease of local repair, and in capability for on-line quality control they represent a much improved match to the needs of developing countries.

Explorations are in train regarding the manufacture of instruments of this type by commercial firms. The outlook, however, is rather pessimistic, presumably because simplicity and low price are suspect virtues in the commercial world. We are also following an alternative approach, namely encouraging atomic energy commissions or other organizations in developing countries to assemble instruments of this sort in their own laboratories; progress is well advanced in one country.

C. Liquid scintillation counters

1. Commercially available instruments

A survey of liquid scintillation counters commercially available as of about 1 January 1978 is also to be found in Attachment 2.

2. Consultants' meeting

A consultants' meeting in February 1978 reviewed the design attributes of liquid scintillation counters that might have highest priority for developing countries. As to the applications of such counters, it was noted that for radioimmunoassays and related in-vitro assays new techniques have made possible labeling with ^{125}I many of the substances (e.g., steroid hormones) which previously were labeled with ^3H ; hence the need for liquid scintillation counters in such fields has shrunk. In view of the probably reduced number of samples and the great importance of simplicity, the consultants in principle favored manual counters for smaller nuclear medicine laboratories that might require liquid scintillation counting. They also recognized that the market for liquid scintillation counters in developing countries was probably not large enough to stimulate manufacturers to develop new lines of instruments for this market alone.

Apparently only one modern manual liquid scintillation counter is at present commercially available, the Nuclear Enterprises (U.S.A.) LSM-1. Tests in our laboratory suggest that certain minor but important modifications are necessary. Thereafter, however, with an efficiency approaching 88 % for ^{14}C and 51 % for ^3H (under optimum conditions), this simple device should be capable of fulfilling most tasks when the number of samples to be assayed is modest and the variability of quenching from one sample to the next is limited. (This counter will be provided under the Agency's technical assistance program as a replacement for an automatic counter that broke down soon after delivery many years ago after measuring samples from a total of 3 rats.)

D. Radiorespirometry

As described above in connection with the identification of rewarding radionuclide applications, radiorespirometry might have a useful role to play in the study of infectious diseases and drug resistance in developing countries. Two investigators of this technique, one from India and one from the U.S., met with us in May 1978 to review its possibilities and the instrumentation it requires. Both of these investigators believed that a technique based on liquid scintillation counting of $^{14}\text{CO}_2$ evolved in a two-compartment closed vial is likely to be preferred over gas counting of $^{14}\text{CO}_2$. For the former technique commercial liquid scintillation counters are very suitable, the automatic sample changing but not automatic quench correction being valuable attributes. New instrument developments required in the counting process seem to be limited to details of the counting vial (which must also serve as the vial in which the organisms are cultured). Reportedly promising innovations will soon be made public after they have been patented.

E. Whole-body counters

While not now widely used in nuclear medicine laboratories in developing countries, whole-body counters could play an important role in certain laboratories studying gastrointestinal absorption and nutrition. One restraint upon their wider use has been the unreasonable complexity and expense of currently fashionable designs.

A consultants' meeting in May 1978 examined the design problems, and concluded that shadow-shield scanning-geometry counters could meet most needs at very low cost. They would be based on one (or two) NaI(Tl) crystals of dimensions about 5" ϕ x 3", a single channel analyzer, and a ton of lead or iron shielding. The consultants are preparing more detailed descriptions of alternative designs and the performance to be expected of them.

F. Electrical power supplies for nuclear medicine instruments

It is common knowledge that low-quality electrical mains power in many laboratories in developing countries may both compromise the results of measurements and also damage instruments. A group of consultants in February 1978 reviewed measures that may be taken to mitigate these effects, either for existing instruments or as innovations in the design of new instruments.

Many protective measures can be taken, but seldom are. A first and inexpensive step should be to assure that electrical power to instruments is supplied, beyond the last step-down transformer, by a power line dedicated to them alone (i.e., no air-conditioners, elevators, etc.), that each group of instruments is grounded by a separate grounding lead planted sufficiently deep in the earth, and that low voltage circuit breakers are connected to prevent electrocution. The next level of protection would depend on both the frequency and the character of power disturbances and on the nature of the instrument or measurement. It might be an assembly consisting of a drop-out relay (which assures that, following a power failure, the instrument is immediately switched off, and following return of power is switched on only after mains stability is reestablished), a surge protector, a constant voltage transformer, and a low-pass filter. For instruments (e.g., those that are computer-based) that cannot tolerate power dropouts, an uninterruptible power supply (UPS) would be needed, probably based on batteries but possibly on a motor-generator set. In the future, direct operation of low power instruments from batteries on float charge is to be desired and may become common. Batteries have undergone substantial improvements in recent years.

These recommendations are being prepared for publication, together with an extensive tabulation of commercially available power conditioning equipment and accessories.

G. Calculators

Our experience with the Hewlett Packard 97 calculator as a component of the Agency's prototype well scintillation counter has been so favorable (virtuosity, low cost, potential availability of service) that we believe such devices could have a special role in instruments for developing countries. Progress in calculators and home computers (increase in capability, decrease in price) is so rapid and so strongly motivated by so many interests as to make futile any intervention by us with regard to hardware. However, we have collected information on the inexpensive systems as they become available. On the side of software we have made a major effort in developing HP-97 programs for radioimmunoassay with our prototype well scintillation counter (q.v.). We have also started an informal collaboration with a group sponsored by WHO that is developing programs to be used off-line on the successor to the HP-97 in quality control of radioimmunoassay.

H. Imaging devices

To date our investigation of imaging instrumentation has been confined to the partial support of one research contract (N. Veall, Medical Research Council Clinical Research Centre, Harrow, Middlesex, U.K.) in which a "hybrid" scanner was developed for liver imaging using $^{113}\text{In}^m$ in The Gambia. This instrument functions in one dimension as a mechanical scanner, wherein the detector mechanically traverses slowly along the length of the patient, and in the transverse dimension as a gamma camera, wherein the position of the scintillation in a long NaI(Tl) detector is determined by comparing the magnitudes of the light flashes emerging from the two ends of the detector. The instrument is thus mechanically simpler than a rectilinear scanner and electronically simpler than a gamma camera, and the radionuclide foreseen is more easily available in developing countries than $^{99}\text{Tc}^m$. Spatial resolution is about 2 cm. Provision is made for operation from an aircraft battery. The device is now in The Gambia awaiting installation.

IV. Maintenance of Instruments

In our previous Progress Report our concept for regional surveys of the state of maintenance of nuclear medicine instruments was described. The survey in Southeast Asia has just been completed, although analysis of the findings is still underway. The surveys in the other 3 regions foreseen - Middle East and

Mediterranean, Africa, Latin America - are in the process of establishment; however, our desire to assure the indigenous character and local management of these surveys has led to substantial delays in their initiation.

The 8 countries participating in the Southeast Asia survey have been listed in Section II.A above. We requested nomination by each government of one individual to coordinate the survey in that country, and negotiated a research contract with each coordinator.

A draft survey design was established by us, and finalized after its review by the national coordinators just before initiation of the survey. In its final form the survey consisted of two parts: (1) questionnaires on the laboratory and on each instrument to be filled out at the start of the survey, and (2) a report on the use, breakdown, and repair history of each instrument during the following period of 6 months.

The questionnaire relating to the laboratory was intended to elicit such information as the following: personnel, instruments, origin and supply of radiopharmaceuticals, equipment available for maintenance, administrative and financial procedures, and types and numbers of radionuclide applications during the past year. The questionnaire relating to each instrument sought data on: type and origin of instrument, cost, availability of service manual, existence of spare parts, existence of maintenance contract, presence of air conditioning, presence of voltage stabilizer, and identity of persons operating and maintaining instrument. In general, these questionnaires were designed to bring out information believed to be important by participants in our 1975 Advisory Group on Maintenance of Nuclear Medicine Instruments in Developing Countries. Many compromises had to be made between our desire for detailed information and our fear of overburdening the responders.

Reports on the events of interest during the 6 month prospective period of observation were of 2 sorts. The first was a daily record of instrument status (ready for use, awaiting repair, or awaiting operating personnel, radionuclides, or consumable supplies). The second was a description of the cause of each period of inoperation and the remedial measures taken.

Each national coordinator was responsible for explaining the survey to the laboratories in his country, and for assuring the timely collection of

accurate data initially and during the 6-month prospective period. Needless to say, various difficulties arose that led to less than perfect results, but on the whole the survey was conducted conscientiously. At its conclusion all national coordinators met to draw lessons from their experience and to discuss possible remedial measures.

The wealth of data collected is now being analyzed in various ways. The barest statistical summary of breakdown and repair experience is given in Table 2 for all countries except India. Overall, of 223 instruments included in the survey from 51 laboratories, 34 % experienced at least one breakdown and 20 % were not returned to service within 7 working days. (Nearly all in the latter category were in fact still not back in service by the end of one month.) This record is perhaps more encouraging than we expected, but a deeper analysis is still required. Spare parts were locally on stock for about a quarter of the instruments; the stated value of these spare parts totalled about \$ 35,000.

Attempts to understand what conditions promoted breakdowns and delayed repairs, and then to suggest remedial measures that might be introduced, can be undertaken from various points of departure. Each national coordinator gave his opinions in a report, and these give prominence to the availability of spare parts and competent servicemen. In addition, a detailed statistical analysis has been started by us to seek correlations among the various revelations of the survey, the hope being to identify in a more objective manner the most important issues. It is too early to know whether statistical analysis will usefully supplement the common-sense appraisal of the results; however, it may form a sounder base for taking corrective action.

Table 1

PROCEDURES WITH RADIONUCLIDES AND RADIOPHARMACEUTICALS

(54 Laboratories)

	<u>Number of labor- atories performing procedure</u>	<u>Total number of procedures/year</u>
<u>ENDOCRINE SYSTEM</u>		
Thyroid uptake	39	50,000
Thyroid imaging	40	35,000
Parathyroid imaging	-	-
Adrenal imaging	-	-
Endocrine System in-vitro assay procedure	29	60,000
<u>HEMATOPOIETIC, RETICULOENDOTHELIAL AND LYMPHATIC SYSTEM</u>		
Bone marrow imaging	3	20
Blood or plasma volume	14	1,000
Red cell mass determination	7	200
Red cell survival study	14	500
Red cell splenic and/or hepatic sequestration	7	100
Radioiron distribution and utilization	9	500
Vitamin B-12, serum folic acid or human hepatitis antigen in-vitro assay procedure	7	3,600
Spleen imaging	17	700
Lymphatics and lymph glands imaging	3	20
<u>GASTROINTESTINAL SYSTEM</u>		
Liver imaging	40	23,000
Liver function	6	2,400
Salivary gland imaging	-	-
Pancreas imaging	5	300
Vitamin B-12 absorption studies	3	100
Gastrointestinal blood loss study	1	50
Gastrointestinal fat or fatty acid absorption study	-	-
Gastrin, intrinsic factor or carcinoembryonic antigen in-vitro assay procedure	3	1,500
Bowel imaging	-	-
Potassium, sodium or other electrolyte studies	-	-
Body water or extracellular fluid volume	2	500
<u>MUSCULOSKELETAL SYSTEM</u>		
Bone imaging	16	600
Joint imaging	1	20
<u>CARDIOVASCULAR SYSTEM</u>		
Cardiac blood pool or myocardium imaging	13	800
Cardiac flow study	3	100

Vascular flow study	1	10
Venous thrombosis study	-	-
Cardiac output	3	300
Tissue clearance studies	-	-
Digoxin or digitoxin in-vitro assay procedure	5	200
<u>RESPIRATORY SYSTEM</u>		
Pulmonary perfusion or ventilation imaging	18	800
<u>NERVOUS SYSTEM</u>		
Brain or cerebrospinal fluid flow imaging	33	10,000
Brain vascular flow	8	1,500
Eye tumor identification with radio-phosphorous	-	-
<u>GENITOURINARY SYSTEM</u>		
Kidney imaging	30	3,000
Kidney function and vascular flow	19	4,100
Renin or angiotensin II in-vitro procedure	7	500
Urinary bladder residual or ureteral reflux study	-	-
Human reproductive hormone in-vitro assay procedure	3	2,300
Placenta imaging	12	900
Placenta localization	2	50
<u>THERAPEUTIC PROCEDURES</u>		
Thyroid radionuclide therapy	21	1,600
Hematological radionuclide therapy	5	90
Intracavitary, interstitial or intra-vascular colloid or particulate radionuclide therapy	6	1,500
Intra-articular radionuclide therapy	-	-
Bone or bone marrow radionuclide therapy	-	-
<u>MISCELLANEOUS</u>		
Morphine in-vitro assay procedures	2	260,000

REPAIR HISTORY OF NUCLEAR MEDICINE INSTRUMENTS IN 51 LABORATORIES

Table 2

Country Code #	01		05		06		07		08		09		10		ALL	
Number of Labs	3		1		5		15		6		2		19		51	
Instrument type	Number of Instruments															
	T	R	T	R	T	R	T	R	T	R	T	R	T	R	T	R
MWS	4	1	2	0	4	1	10	3	3	1	2	1	8	1	33	8
AWS	0	0	2	1	1	1	4	3	4	0	0	0	11	6	22	11
MLS	0	0	0	0	0	0	1	1	0	0	0	0	0	0	1	1
ALS	1	1	1	1	1	0	1	1	2	2	1	0	6	4	13	9
RCa	2	0	1	0	5	1	13	4	0	0	1	1	10	1	32	7
SPS	3	2	2	0	6	1	15	3	1	0	1	1	8	2	36	9
DPS	3	2	1	0	3	0	2	1	0	0	1	1	9	3	19	7
Sca	3	2	3	0	7	0	12	4	1	0	2	2	19	8	47	16
GCa	0	0	0	0	4	2	4	3	1	0	0	0	4	2	13	7
Misc.	3	0	0	0	0	0	2	0	0	0	0	0	2	1	7	1
All	19	8	12	2	31	6	64	23	12	3	8	6	77	28	223	76 (34 %)
Repair <7 days		4		1		3		5		3		0		15		31 (14 %)
Repair >7 days		4		1		3		18		0		6		13		45 (20 %)

T Total number of instruments surveyed
 R Number of instruments involved in repair
 MWS Manual well counter
 AWS Automatic well counter
 MLS Manual liquid scintillation counter
 ALS Automatic liquid scintillation counter

RCa Radioisotope calibrator
 SPS Single probe system
 DPS Dual or multiple probe system
 Sca Rectilinear or whole-body scanner
 GCa Gamma camera
 Misc Miscellaneous instruments

Accounting of Staff Effort

Four professional staff members have participated in this project at approximately the following percentages of their time:

<u>Name</u>	<u>Section</u>	<u>% of time</u>
R.A. Dudley	Medical Applications	60 %
B. Hoop	"	90 %
A.C. Morris	"	100 %
E.A. Kerroe	Electronics	20 %

Technical staff in the electronics and mechanical workshop have contributed another 2 man years during the current contract year.

Published Reports

Well scintillation counting systems for nuclear medicine applications in developing countries, IAEA-201, 1977 (Attachment 3).

A.C. Morris and R.A. Dudley, "Characteristics of commercially available well scintillation counting systems and liquid scintillation counting systems", in Radioimmunoassay and Related Procedures in Medicine, v. I, p. 517, IAEA, Vienna, 1978 (Attachment 2).

Dudley, R.A., Figdor, H.C., Kerroe, E.A., Morris, A.C.Jr., Mutz, O.J., "Well scintillation counter with automatic sample changing and data processing: an inexpensive instrument incorporating consumer products", in Radioimmunoassay and Related Procedures in Medicine, v.I, p. 457, IAEA, Vienna, 1978 (Attachment 4).

(In addition, numerous unpublished reports have become available at consultants' meetings, e.g. Attachment 1).

Cost-Effectiveness Analysis of RIA and CEP in Screening
Blood-Donor Blood for Hepatitis B Surface Antigen

I. Introduction

The ultimate purpose of this investigation is to determine by cost-effectiveness analysis the circumstances under which screening by radioimmunoassay for hepatitis B surface antigen (HbsAg) in blood collected for transfusion is appropriate in developing countries. Initially, however, the scope is restricted to a comparison of RIA on the one hand, and CEP (counter-electrophoresis) or no testing on the other hand, in India. Since the data available appear inadequate to give clear guidance even in this limited context, the immediate goal of this study is to determine what additional data are needed and potentially available to permit such decisions to be made rationally.

Hepatitis in general (including A, B, and non-A non-B) is a health problem of considerable importance in India: Pattanayak et al. (1973) estimated that there were nearly half a million cases in the entire country (103 cases per 100,000 population). A similar estimate can also be obtained by extrapolating data from a partial survey of 22 states by the Indian Ministry of Health which indicated that there were 118,882 new cases of hepatitis in 1975 and 1197 associated deaths.

Not all cases of hepatitis require hospitalization and data on the overall rate of hospitalization are lacking. In general, however, large general public hospitals such as the Safdarjang Hospital in Delhi and the JJ Group of Hospitals in Bombay appear to have about 200 cases per year (five cases per 1000 new admissions) with an average length of stay of 14 days and a mortality of 10 % (Pattanayak et al., 1973). At specialized infectious disease hospitals both the number of admissions and the length of stay are longer - there the proportion of admissions for hepatitis may be as high as 25 %, and the average length of stay, six to eight weeks. At the Kasturba Infectious Disease Hospital in Bombay, for example, there are about 3000 annual admissions for hepatitis and at an analogous hospital in Madras there were in one year 6179 admissions (Madanagopalan, 1973).

Estimates of the proportion of all cases of hepatitis that are type B vary from 12 - 40 % (Pattanayak et al., 1973; Pal et al., 1974; Sharma et al., 1976; Banerjee, verbal estimates, 1977). Since hepatitis B can be transferred by the parenteral or non-parenteral route, however, not all of this hepatitis B is secondary to transfusions. Approximately 10 % of transfused patients develop icteric hepatitis (John et al., 1974; Banerjee, verbal estimates, 1977) and, therefore, on the basis of data from the U.S. Veterans Administration, the percent of transfused patients developing either icteric or anicteric hepatitis may be as high as 40 - 50 % (Seeff et al., 1977).

Screening of blood-donor blood for HbsAg is now performed almost universally in many developed countries as a means of reducing transmission of hepatitis B through blood transfusion. So-called "second-generation tests" (e.g., counter-electrophoresis (CEP) or reversed passive latex agglutination (RPLA)) have tended to be replaced by "third-generation tests" (e.g., RIA or reversed passive hemagglutination assays (RPHA)), and new tests continue to be devised. In Europe in 1975 the RIA test for HbsAg ranked, as a share of the market, ahead of all other radioisotope in-vitro tests, outranking all such thyroid-related in-vitro tests combined (Arnold, 1975). RIA is as yet little used for hepatitis B screening in India.

The strategy adopted in this analysis of the value of screening is (1) to define a model of hepatitis transmission through blood transfusion, as influenced by screening, (2) to estimate numerical values for the numerous parameters embodied in the model as judged to be relevant in India, (3) to calculate the health and financial consequences of testing according to the model, and (4) in view of the uncertainty of the numerical values of the parameters and hence of the results, to use these preliminary results to identify the critical parameters whose values should be further investigated.

II. The model

The model for blood screening by RIA or CEP is shown in Fig. 8. After each blood unit is collected at a cost C , it is tested at a cost T . A fraction P (the "carrier rate") of the collected units carries HbsAg; the remaining fraction, $1-P$, does not. Of those units that do carry HbsAg, a fraction p is correctly detected as positive ("true positive") by the test and discarded. Of those units that do not, a fraction q is erroneously detected as positive ("false positive") and also discarded. Each unit carrying HbsAg but not

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screened out ("false negative") has a probability b of causing hepatitis B in the recipient. The average health cost of a case of hepatitis B is defined as H . In principle H embraces all health costs, including not only treatment but also financial losses to society associated with sickness and death; obviously H will be difficult to quantify. Each of these parameters except C and P may take on different numerical values for different tests; they are therefore subscripted 2 for CEP (i.e., second generation) and 3 for RIA (i.e., third generation). Values obtaining when no test is applied are subscripted 0 (i.e., zeroth generation). These symbols are defined more precisely in Appendix 1.

The analysis is based upon the assumption that a sufficient number N_1 of blood units is collected to yield under all testing regimes N ($= 10,000$) units of blood accepted for transfusion.

Mathematical expressions may be deduced for all the health and financial consequences of transfusion and screening that flow as a logical consequence from this model. The expressions used in this analysis are derived in Appendix 2. It may be discouraging that these expressions are so numerous and complex. However, their derivation is straightforward and their numerical values can be quickly calculated on a programmable calculator. Furthermore, the complexity is in part illusory: most expressions are linear in C , T , H , and b .

The first question one asks about the model is whether it is realistic. It is hard to see how it could be unrealistic regarding the transmission of hepatitis B through transfused blood, the specific subject of this study. However, it must be borne in mind that this issue does not constitute the whole hepatitis story. For one thing, Seeff et al. (1977) reported from a multicenter study in which aliquots of transfused blood were subsequently screened by RIA that among patients who received RIA-negative blood, those who acquired hepatitis B were over 10 times as numerous as those who could have received actually positive blood (i.e., RIA false-negative units) if the sensitivity p of the RIA test was the 98 % believed. To be sure, even the observed rate was rather low in absolute terms - presumably it reflects some "background" transmission of hepatitis B associated not with transfused blood but with proximity to doctors or some other aspect of life in Veterans Administration hospitals. Second, other forms of hepatitis than hepatitis B can also be transmitted through transfusion. It has been suggested that such

other forms of hepatitis may occur preferentially in individual donors carrying hepatitis B, so that screening out hepatitis B brings as a bonus a reduced transmission of other forms of hepatitis also. In the data of Sccff et al. (1977) there is little evidence for this bonus. Thus of 48 patients who received blood that subsequently was found to be RIA-positive for HbsAg, 5 (10 %) developed non-B hepatitis. Of 960 receiving RIA-negative blood, 91 (9 %) developed non-B hepatitis. Clearly, such scanty data cannot disprove the existence of a hypothesized bonus.

The second question one asks about the model is whether the parameters it embodies can be given realistic numerical values. This is examined in the next section. Obviously it will be a difficult task, as data are scarce and many of the parameters will vary substantially according to the environment. However, proclaiming that to ignore uncertainty does not establish its non-existence, the cost-effectiveness analyst attempts to quantify it. In any case, a serious study must soon proceed to the substitution of numbers into the equations, since a decision as to whether parameter x or y is more important may depend on the absolute magnitude of parameter z.

III. Numerical values of the parameters in India

From the data available, numerical values are selected below to be used for the 14 parameters in subsequent calculations. Also, an estimate is given for the "plausible range" within which the values might be expected to lie. A primary task of future analyses of this problem will be to refine the values of these crude numerical estimates (or guesses).

1. P

According to Pal et al. (1974) and John et al. (1974), 2.3 - 4 % of voluntary blood donors and 8 % of professional donors in India have been found positive for HbsAg by second generation tests. Assuming these tests to have a p_2 of 67 % (see below), the true carrier rates would scale up to 3.4 - 6 % and 12 % respectively. It must be assumed that different communities will have different average rates. Numerical data subsequently calculated assume $P = 10$ %, with a "plausible range" of 3 - 15 %.

2. p_2

In the U.S., second generation tests are believed to detect about 2/3 of sera positive by third generation tests (Gerety et al., 1975). A value of 67 % is assumed for India, "plausible range" 55 - 75 %.

3. p_3

In the U.S., sample test panels using third generation tests identify approximately 98 % of sera known to be positive for HbsAg (Gerety et al., 1975). The same figure is assumed for India, with a "plausible range" of 95 - 99 %.

4. q_2

In the U.S., a false positive rate of 5 % has been estimated for second generation tests (Gerety et al., 1975); this value is assumed below for India, with a "plausible range" of 2 - 10 %.

5. q_3

Values have been estimated in the U.S. of about 0.1 - 2.7 % (Abbott Laboratories, 1976; Gerety, 1975), the higher values being reduced somewhat if apparent positives are retested, and discarded only if the second test is also positive. In India it is apparently cheaper to discard after a single positive test and to collect and test a new unit of blood, rather than to retest positives. A value of 2.7 % is assumed below, "plausible range" 1 - 5 %.

6. C

It is assumed that in India, as in the U.S., the cost of collecting blood is approximately equal to the price paid for commercial blood, or Rs. 15 (\$ 1 $\approx$ Rs. 8); the "plausible range" is taken as Rs. 10 - 30.

7. T_2

In the U.S., second generation tests commercially purchased cost about \$ 0.50 for materials and \$ 1.00 for labor. At the Tata Blood Bank in Bombay, the overall cost, including glassware, chemicals, imported medium for electrophoresis and imported antiserum, and the labor of 1 technician to process 10,000 blood units/year, amounts to Rs. 10 per test (Nair, 1977). This value is assumed below, with a "plausible range" of Rs. 5 - 15.

8. T_3

It is assumed that in India, as in the U.S., third generation tests cost 1.5 times as much as second generation tests, i.e. Rs. 15. The "plausible range" is taken as Rs. 10 - 30.

9. bH

In all equations in Appendix 2 that are useful for comparing diagnostic and health-consequence costs, the parameters b and H appear as a product - i.e., the health costs (in monetary terms) of transfusing a unit of blood carrying HbsAg. However, it is probably easier to extrapolate bH across cultural boundaries by considering b and H separately.

9a. b

Definitions as to what degree of biochemical abnormality is required before "type B infection" is called "type B hepatitis" probably vary. Here the definition used by Seeff et al. (1977) is implicitly assumed (q.v.).

Seeff et al. reported that of 16 subjects who received one or more transfusions of unscreened blood that was subsequently established by RIA as positive, 4 developed hepatitis B ($b_0 = 25\%$). Similarly, of 32 who received blood classified negative by CEP screening but subsequently found by RIA to be positive, 4 developed hepatitis B ($b_2 = 12.5\%$). They give no data bearing on b_3 (except, as previously noted, the evidence that so many subjects who have received RIA-negative blood develop hepatitis B as to establish some etiology in addition to blood transfusion). If b_2 is really less than b_0 , presumably b_3 is less than b_2 . These numbers have limited statistical reliability, and in any case cannot be assumed to be valid in other societies having different levels of virulence in donors and immunity in recipients. Calculations are performed below for $b_0 = 25\%$. For the ratios $r_2 \equiv b_2/b_0$ and $r_3 \equiv b_3/b_0$, three pairs of values have been used:

$$\begin{aligned} r_2 &= 100\%, & r_3 &= 100\% \\ r_2 &= 70\%, & r_3 &= 50\% \\ r_2 &= 50\%, & r_3 &= 25\%. \end{aligned}$$

For the final table, Table 2, the following assumptions have been used:

$$\begin{aligned} b_0 &= 25\%, \text{ "plausible range" } 15 - 40\% \\ r_2 &= 70\%, \text{ "plausible range" } 50 - 90\% \\ r_3 &= 50\%, \text{ "plausible range" } 30 - 70\%. \end{aligned}$$

9b. H

The value of this parameter is the most ambiguous of all, inasmuch as it involves, beyond the usual uncertainties, philosophical judgements as to the

cost of sickness and death. While H , like b , may be different for different screening tests (e.g., $H_3 < H_2$ because those who contract hepatitis B from RIA-screened blood may not become as sick as those who contract it from CEP-screened blood), it is assumed below that $H_0 = H_2 = H_3 = H$. This restriction can be easily lifted by dealing only with the product bH , and considering the variability of H and b to be jointly embedded in the ratios r_2 and r_3 .

Data in Seeff et al. on percentages of hepatitis cases requiring hospitalization show 38 % (5/13) for those who received positive blood and 16 % (18/116) for those who received negative blood. Since these hepatitis cases are an unknown mixture of type B and type non-B, the data are of little use. Anyway, they would scarcely apply unaltered to India. If 20 % of post-transfusion hepatitis B cases in India are hospitalized, each for 14 days at Rs. 37/day, the average cost per hepatitis B case would be Rs. 104. Obviously this would be only a fraction of H , which includes all health costs.

In the calculations below it is assumed that $H = \text{Rs. } 837.236 (!)$, this being the value that would allow CEP-testing just to pay off in the presence of the values here assumed for all the other parameters. The "plausible range" is taken as Rs. 200 - 2000, the lower "limit" being taken as twice the aforementioned hospitalization costs and the upper "limit" as the value required to justify CEP-testing if $P = 3 \%$ (as it may in some Indian communities where CEP-testing is now performed) and the other parameters have the values here assumed.*

IV. Health and financial consequences of testing

The consequences of testing according to the model are shown in Table 1b, using the foregoing numerical estimates of the parameters (as summarized in Table 1a). For comparison, the implications of no testing are included. For all 5 regimes (columns 1 - 5), 10000 units of blood are assumed to be transfused, with no more than 1 contaminated unit given to any one patient (e.g., as with one transfusion per recipient, or with several units per patient but a very low residual contamination rate after screening). In Table 1b results are given only for a single set of parameters. In the following section the sensitivity of the most important of these results to shifts in the value of the parameters is explored.

*For the reader who at this point despairs: (1) This analysis does not create the uncertainty in H ; it will merely seek to display its implications.
(2) There is a little bit of good news ahead.

Among the "transfusion and health parameters", the most interesting is the number of cases of hepatitis B caused. Screening clearly has a beneficial effect, RIA more than CEP, low r more than high r . RIA with $r_3 = 25\%$ is an almost perfect test.

The monetary costs are expressed as an average per transfusion; they include blood collection, blood testing, and (lumped together on the other side of the balance sheet) all costs of treatment, ill health, and death associated with transfusion-caused hepatitis D.

The meaning of the subsequent financial concepts is made precise in the equations referenced (see Appendix 2). The goal of screening is to achieve a net benefit ≥ 0 , i.e., total costs less than the Rs. 35.93 per transfusion associated with no testing. The magnitude of H was chosen so as to give $\overline{NB}_2 = 0$ when $r_2 = 100\%$ (column 2). The other 3 conditions happen to give a small positive net benefit.

In column 2 the marginal diagnostic cost per hepatitis B case averted (as compared with no testing) is Rs. 837.3. When the average health cost (H) of a case of hepatitis B just equals the cost of averting a case, the net benefit of testing is zero. This is the situation in column 2. For the other 3 testing regimes the cost of averting a case is less than the assumed value of $H = \text{Rs. } 837.3$; therefore their net benefit must be positive. The next row shows the same thing, but as a ratio to H of the cost of averting a case of hepatitis B; when the ratio is less than unity, the net benefit must be positive.

The so-called "equivalence test cost" has some interesting, and perhaps subtle, implications. This is the cost of test 3 which would give the same effect as test 2, per unit extra cost (beyond no testing) for collecting and testing blood - i.e., the same ratio of effect to cost. Under these conditions the upper limit of the cost which test 3 may assume in order for it to remain competitive with test 2 can be determined even when H is unknown, since H cancels out on the two sides of the equation.

Equations 12 and 12a can be derived by another route which is perhaps more transparent and more informative. In column 2 of Table 1b it is seen that test 2 results in 92.9 hepatitis B cases per 10000 transfusions, compared with 250 for no testing. The same reduction could alternatively be achieved by taking only a part of the 10000 required units from RIA-tested blood and the rest from untested blood. For example, under the conditions of columns 1 and 3 one would take 6430 units of RIA-tested blood and 3570 units of

untested blood to produce the same effect as CEP: 92.9 cases of hepatitis B. One would then solve for the testing cost of RIA that would give the same collection-plus-testing costs as CEP, and find $T_{3,2} = \text{Rs. } 16.12$ just as from Eq. 12a. If T_3 were in fact less than Rs. 16.12, one would say RIA is certainly preferable to CEP, irrespective of the unknown (unknowable?) value of H. One's joy at thus shedding H must however be restrained. One now has the same effect at less cost - the cost-effectiveness analyst's dream - but the net benefit may still be negative. If one adopted this peculiar testing procedure, 64 % tested by RIA and 36 % untested, he would indeed not have as large a negative balance as with CEP. However, no laboratory would adopt this procedure. It would instead test 100 % by RIA, and if the net benefit were negative at 64 % testing it would be still more negative at 100 % testing, perhaps now more negative than when CEP was used! In other words, advice that a laboratory switch from CEP to RIA on the grounds that $T_3 < T_{3,2}$ is assuredly good advice only if the net benefit under CEP is already positive. Furthermore, if $T_3 > T_{3,2}$, one cannot be sure that a switch from CEP to RIA is inappropriate; this depends upon H. Thus H has been only partially shed.*

Finally, the breakeven test cost is that which gives a net benefit of 0; a lower test cost is assured of giving a positive net benefit. Since, for example, in column 3 of Table 1b the assumed test cost for RIA is Rs. 15, less than the calculated breakeven cost of Rs. 16.12, there must be a positive net benefit in this testing regime.

* One could define yet another equal cost situation, namely the value $t_{3,2}$ of T_3 such as to give equal costs for collection plus testing for CEP and RIA. Thus from Eqs. 5 and 6:

$$\frac{C}{R_3} + \frac{t_{3,2}}{R_3} = \frac{C}{R_2} + \frac{T_2}{R_2}, \text{ or } t_{3,2} = C\left(\frac{R_3}{R_2} - 1\right) + \frac{R_3}{R_2}T_2.$$

The quantity $t_{3,2}$ is certainly independent of H, and if $T_3 < t_{3,2}$, then there can be no doubt that switching from CEP to RIA is justified. However, it is hard to see how one would in practice use this criterion. If one believed that the CEP test now employed had a positive net benefit, he could use the less stringent criterion that T_3 must be less than $T_{3,2}$. If he believed that CEP as now employed had a negative net benefit, his proper advice would probably be to abandon testing altogether rather than switch to RIA with a negative net benefit of slightly smaller magnitude. In any case, under these latter circumstances an examination of $\overline{NB}_3$ per se could not safely be avoided.

V. Critical parameters in comparing RIA with CEP

If one finds the conclusions in Table 1b less than compelling, but is not so despondent as to give up, he will ask which parameters are worth refining. If most of the values assumed for the parameters are realistic, then observing the effect on, for example, average net benefit as individual parameters are varied one at a time will be informative. If most values are however unrealistic, then the process will unfortunately be a futile search for an optimum in some irrelevant corner of 14-dimensional space.

In Table 2 are collected data that display the sensitivity of the results to the uncertainty in the individual parameters. In column 1 the parameters are listed, in column 2 their finally assumed values, and in column 3 their "plausible ranges" as guessed in Section III.

Columns 4 and 5 of Table 2 pertain to the equivalence test cost, $T_{3,2}$. Column 4 is the derivative of $T_{3,2}$ (Eq. 12) with respect to the individual parameters, evaluated at the assumed values of each of these parameters. Column 5 is the absolute value of one half the product of the "plausible range" and the derivative, i.e., one half the resultant uncertainty in the absolute value of Rs. 13.6 calculated for the equivalence test cost using the assumed values of the parameters. Crudely speaking, for example, one would say that the uncertainty in P causes an uncertainty of $\pm$ Rs. 0.3 in the estimated value of $T_{3,2} = \text{Rs. } 13.6$.

The equivalence test cost is seen to be a surprisingly robust quantity, independent of uncertainties not only in H but also in b_0 , and nearly independent of uncertainties in P, C, p_3 , q_3 , and r_3 . The altogether dominant uncertainty is T_2 . The approximate analytic dependence of $T_{3,2}$ on the parameters is shown in Eq. 12a, which with p_1 large and q_1 small reduces to $\frac{T_{3,2}}{p_3} \approx \frac{T_2}{p_2}$. Indeed, spoil-sports will note that this could have been written down intuitively, without the aid of mathematics. In Fig. 1, $T_{3,2}$ is plotted against P for $r_2 = r_3 = 100\%$ (curve A) and $r_2 = 50\%$, $r_3 = 25\%$ (curve B).

In Table 2, columns 6 and 7 pertain to $\overline{NB}_3$, column 6 (analogous to column 4) being its derivative with respect to the parameters and column 7 (analogous to column 5) being the resultant "one-half uncertainty" attributable to the parameters. The uncertainty in $\overline{NB}_3$ is dominated by the uncertainty in 4 parameters: H , b_o , P and T_3 . All other uncertainties contribute almost negligibly, and this dichotomy appears quite secure. Figs. 3b - 6b show the dependence of $\overline{NB}_3$ on these 4 parameters when they are allowed to vary one at a time while all others but this one are held constant at the values shown in Table 2, column 2. Curves A are again for $r_2 = r_3 = 100\%$, and curves B for $r_2 = 50\%$, $r_3 = 25\%$. Where $\overline{NB}_3 = 0$, the independent parameter may be said to be at its "breakeven value". For example, in Fig. 5b T_3 has its breakeven value, T_{B3} , at 16.1 for curve A (see Table 1b, column (3)). Or similarly in curve 4b, P has its "breakeven value" at about 9.5%. For test 3, curves A and B are very close together: since p_3 is so near unity, the test is nearly perfect and it makes little difference whether r_3 is large or small (as confirmed in Table 2, column 7). Fig. 2b shows a plot of the breakeven test cost T_{B3} against P in a different slice through 14-dimensional space.

Columns 8 and 9 of Table 2 show the same information for $\overline{NB}_2$ as do columns 6 and 7 for $\overline{NB}_3$. Similarly, Figs. 2a - 6a are analogous to Figs. 2b - 6b. Once again the dominant uncertainties are contributed by H , b_o , P , and the relevant test cost T_2 .

Finally, Figs. 7a and 7b show the values of H that would give $T_{B2} = \text{Rs. } 10$ and $T_{B3} = \text{Rs. } 15$, as a function of P . These are the implicit values of health costs that (no doubt unknown to transfusion services) must be exceeded if testing for HbsAg is to pay off - assuming other parameters have values as shown in column 2, Table 2.

VI. Conclusions

The foregoing analysis (which cynics may claim treats only the obvious or the unknowable) suggests the following:

(1) On the basis of present evidence, it is not clear that a switch from CEP to RIA testing would be justified, nor even that CEP testing should be continued.

(2) The dominant uncertainty, not surprisingly, lies in the monetary value H of avoiding the sickness and death associated with transfusion-induced hepatitis B. With the exception noted in (3) below, any purported clarification of the overall picture by refining the values of other parameters will be largely illusory unless H is satisfactorily dealt with.

(3) Even the question as to the relative merits of CEP and RIA can be only partially isolated from H , but under circumstances where this is possible the overriding remaining uncertainty is in the relative test costs, T_2 and T_3 . This uncertainty could be greatly reduced, first by a closer analysis of existing data, second by collection of new data. It is not inconceivable that T_3 could be greatly reduced from presently assumed values, first by indigenous production of reagents, second by adopting cheaper procedures that accepted sacrifices in q_3 and especially p_3 , which may now be unnecessarily good, and third by the use of cheaper counting equipment (e.g., the Agency's automatic counter).

(4) Beyond H , T_2 , and T_3 , the most important remaining uncertainties are in P and b_0 . P could be adequately established by properly performed RIA tests on a representative sample of perhaps 300 donors from the relevant donor population of each transfusion service. b_0 will be hard to refine because of ethical problems; however, opportunities might arise to study the drop in hepatitis B transmission after establishment of a screening service where such did not previously exist.

(5) Progress in resolving these questions will be made only when they are pursued by investigators in the developing countries who are convinced that the questions are important.

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Table 1a - Consequences and Financial Implications of Screening:
Values Assumed for Parameters

P	10 %
b ₀	25 %
H	Rs. 837.3
P ₂	67 %
P ₃	98 %
q ₂	5 %
q ₃	2.7 %
T ₂	Rs. 10
T ₃	Rs. 15
C	Rs. 15
r ₂	(as specified above respective column of results)
r ₃	(as specified above respective column of results)

Table 1 b - Consequences and Financial Implications of Screening:

Results of Calculations

	(1) No test	(2) Test 2 (CEP) ($r_2 = 100\%$)	(3) Test 3 (RIA) ($r_3 = 100\%$)	(4) Test 2 (CEP) ($r_2 = 50\%$)	(5) Test 3 (RIA) ($r_3 = 25\%$)
<u>Transfusion and health parameters</u>					
No. units transfused	10,000	10,000	10,000	10,000	10,000
No. donors screened (Eq. 1)	-	11,261	11,393	11,261	11,393
No. units discarded (Eq. 2)	-	1,261	1,393	1,261	1,393
No. inappropriate discards (Eq. 3)	-	507	277	507	277
No. cases hepatitis B caused (Eq. 4)	250	92.9	5.7	46.5	1.42
<u>Average monetary costs (per transfusion)</u>					
Blood collection (Eq. 5) (Rs.)	15.00	16.89	17.09	16.89	17.09
Testing (Eq. 6) (Rs.)	-	11.26	17.09	11.26	17.09
Health costs (Eq. 7) (Rs.)	20.93	7.78	0.28	3.89	0.12
Total (Eq. 8) (Rs.)	35.93	35.93	34.66	32.04	34.30
<u>Average net benefit (per transfusion) (Eq. 9b, 9a) (Rs.)</u>	-	0.00	1.27	3.89	1.63
<u>Marginal diagnostic cost</u>					
Per case averted (Eq. 10b, 10a) (Rs.)	-	837.3	785.1	646.2	771.6
Per unit of health cost (Eq. 11b, 11a)	-	1.00	0.938	0.772	0.922
<u>Equivalence test cost ($T_{3,2}$) (Eq. 12a, 12) (Rs.)</u>	-	-	16.12	-	12.26
<u>Breakeven test cost (T_{Bi}) (Eq. 13a, 13) (Rs.)</u>	-	10.00	16.12	13.45	16.43

Table 2

Sensitivity of Results to Uncertainty of Parameters

Parameter (1)	Value of Parameter (2) Assumed (3) Plausible range		Equivalence Test Cost (Rs.) (Value = Rs. 13.6) Derivative 1/2 Uncertainty (4) (5)		Average Net Benefit ₃ (Rs.) (Value = Rs. 1.51) Derivative 1/2 Uncertainty (6) (7)		Average Net Benefit ₂ (Rs.) (Value = Rs. 2.33) Derivative 1/2 Uncertainty (8) (9)	
H	Rs. 837.3	Rs. 200-2000	-	-	0.025	22	0.019	17
b ₀	25 %	15 - 40 %	-	-	0.83	10	0.62	8
P	10 %	3 - 15 %	-0.044	0.3	1.70	10	1.31	8
T ₂	Rs. 10	Rs. 5-15	1.32	7	-	-	-1.13	6
T ₃	Rs. 15	Rs. 10-30	-	-	-1.14	11	-	-
C	Rs. 15	Rs. 10-30	0.026	0.3	-0.14	1.4	-0.13	1.3
q ₂	5 %	2 - 10 %	0.39	1.6	-	-	-0.34	1.4
q ₃	2.7 %	1 - 5 %	-0.30	0.6	-0.35	0.7	-	-
p ₂	67 %	55 - 75 %	-0.12	1.2	-	-	0.13	1.3
p ₃	98 %	95 - 99 %	0.056	0.1	0.080	0.2	-	-
r ₂	70 %	50 - 90 %	0.078	1.6	-	-	-0.078	1.6
r ₃	50 %	30 - 70 %	-0.004	0.07	-0.005	0.1	-	-

Fig. 2a

Fig. 3a

Fig. 2b

Fig. 3b

Fig. 4a

Fig. 5a

Fig. 6a

Fig. 7a

Fig. 4b

Fig. 5b

Fig. 6b

Fig. 7b

H (Rs.) for $T_{B2} = \text{Rs. } 10$

$\overline{NB}_2$ (Rs.)

$\overline{NB}_2$ (Rs.)

$\overline{NB}_2$ (Rs.)

H (Rs.) for $T_{B3} = \text{Rs. } 15$

$\overline{NB}_3$ (Rs.)

$\overline{NB}_3$ (Rs.)

$\overline{NB}_3$ (Rs.)

Fig. 8

Cost/unit = C
Carrier rate = P

Cost/test = T_i
True positive fraction = p_i
False positive fraction = q_i

Cost/case = H_i

Appendix 1 - Summary of Symbols for Basic Parameters

i Subscript identifying relevant screening test:

- 0 implies no screening test
- 2 " second generation (CEP) test
- 3 " third generation (RIA) test

P Fraction of collected blood units actually positive for HbsAg (i.e., carrier rate)

p_i True-positive probability for screening test i , i.e., probability that a blood unit positive for HbsAg will be classed as such by test i . (Note: $p_0 = 0$.)

q_i False-positive probability for screening test i , i.e., probability that a blood unit negative for HbsAg will be classed as positive by test i . (Note: $q_0 = 0$. Also note: $q \neq 1-p$.)

R_i $1 - Pp_i - (1-P)q_i$ (see Eq. 1a in Appendix 2). (Note: $R_0 = 1$.)

C Cost of collecting one unit of blood.

T_i Cost of testing one unit of blood by test i . (Note: $T_0 = 0$.)

b_i Probability that a blood unit falsely classed as negative by test i will, upon transfusion, cause hepatitis B in the recipient.

H_i Average "health cost" (expressed in monetary units) of one case of transfusion-caused hepatitis B subsequent to screening by test i . (Note: this is to include all hospitalization and treatment costs, and the costs to society of sickness and death.)

r_i $\frac{b_i H_i}{b_0 H_0}$ ($= \frac{b_i}{b_0}$ if $H_i = H_0$)

N Notional number of blood units transfused (taken as 10000 in all calculations)

N_i Number of blood units collected so as to yield N units for transfusion subsequent to testing by test i . (Note: $N_0 = N$.)

Appendix 2 - Equations

The symbols of basic parameters used in these equations are defined in Appendix 1. A few additional symbols are defined below as they are introduced for convenient representation of derived quantities. All equations in which the right hand side is reduced all the way to the basic parameters (including, however, R) are identified by an asterisk. This complete reduction displays explicitly the dependence of the expression on these basic parameters.

1. To obtain the N units of blood for transfusion subsequent to screening (if any), N_i donor blood units must be collected.

$$N = N_i - (\text{true-positive discards}) - (\text{false-positive discards}) \quad (1)$$

$$= N_i - N_i P p_i - N_i (1-P) q_i = N_i R_i \quad \text{if}$$

$$1 - P p_i - (1-P) q_i = R_i$$

$$\text{Therefore } N_i = \frac{N}{R_i} \quad (1a)^*$$

2. The number of units discarded = $N_i - N$ (2)

$$= \frac{N}{R_i} [P p_i - (1-P) q_i] \quad (2a)^*$$

3. The number of units wrongly discarded (i.e., false-positive discards, as already used in Eq.1)

$$= N_i (1-P) q_i \quad (3)$$

$$= \frac{N}{R_i} (1-P) q_i \quad (3a)^*$$

4. The number n_i of cases of hepatitis B caused by the transfused blood is given by

$$n_i = (\text{false negatives}) \times b_i \quad (4)$$

$$= N_i P (1-p_i) b_i$$

$$= \frac{N}{R_i} P (1-p_i) b_i \quad (4a)^*$$

5. The average cost, per transfusion, of blood collection is

$$\frac{C N_i}{N} = \frac{C}{R_i} \quad (5)^*$$

6. The average cost, per transfusion, of diagnostic testing is

$$\frac{T_i N_i}{N} = \frac{T_i}{R_i} \quad (6)^*$$

7. The average cost, per transfusion, of transfusion-induced hepatitis B cases is

$$\frac{H_i n_i}{N} = \frac{1}{R_i} P(1-p_i) b_i H_i \quad (7)*$$

8. Average total costs, per transfusion, equal the sum of collection, testing, and hepatitis B average costs

$$= \frac{1}{R_i} [C + T_i + P(1-p_i) b_i H_i] \quad (8)*$$

9. Average net benefit, $\overline{NB}_i$, when test i is used as compared with no test is

$$\overline{NB}_i \equiv \frac{1}{N} [\text{Total costs}_0 - \text{Total costs}_i] \quad (9)$$

$$= C(1 - \frac{1}{R_i}) + P[b_o H_o - \frac{(1-p_i)}{R_i} b_i H_i] - \frac{T_i}{R_i}$$

$$= C(1 - \frac{1}{R_i}) + P b_o H_o [1 - \frac{(1-p_i)}{R_i} r_i] - \frac{T_i}{R_i} \quad (9a)*$$

$$\text{where } r_i \equiv \frac{b_i H_i}{b_o H_o}$$

Special case: $b_o H_o = b_i H_i = bH$

$$\overline{NB}_i = C(1 - \frac{1}{R_i}) + PbH[1 - \frac{(1-p_i)}{R_i}] - \frac{T_i}{R_i} \quad (9b)*$$

10. Marginal diagnostic cost per case averted, L_i , is the cost of collecting and testing N_i units of blood when procedure i is used, over and above the cost of collecting N units of blood when no test is performed, divided by the number of hepatitis B cases averted by the testing.
Thus

$$L_i \equiv \frac{N_i(C + T_i) - NC}{n_o - n_i} \quad (10)$$

$$= \frac{C(\frac{1}{R_i} - 1) + \frac{T_i}{R_i}}{P[b_o - \frac{(1-p_i)}{R_i} b_i]} \quad (10a)*$$

Special case: $b_o = b_i = b$

$$L_i = \frac{C(\frac{1}{R_i} - 1) + \frac{T_i}{R_i}}{Pb[1 - \frac{(1-p_i)}{R_i}]} \quad (10b)*$$

11. Marginal diagnostic cost per unit of health cost averted, M_i , is the cost of collecting and testing N_i units of blood when procedure i is used, over and above the cost of collecting N units of blood when no test is performed, divided by the health costs averted by the testing. Thus

$$M_i = \frac{N_i(C + T_i) - NC}{n_o H_o - n_i H_i} \quad (11)$$

$$= \frac{C(\frac{1}{R_i} - 1) + \frac{T_i}{R_i}}{Pb_o H_o [1 - \frac{(1-p_i)}{R_i} r_i]} \quad (11a)*$$

Special case: $b_o H_o = b_i H_i \equiv bH$

$$M_i = \frac{C(\frac{1}{R_i} - 1) + \frac{T_i}{R_i}}{PbH(1 - \frac{(1-p_i)}{R_i})} \quad (11b)*$$

12. Equivalence test cost, $T_{3,2}$, is defined as that cost for test 3 which gives $M_3 = M_2$ (for the value of T_2 and other parameters obtaining). Thus when $T_3 = T_{3,2}$, $M_3 = M_2$, and substituting from Eq. 11a and solving for $T_{3,2}$:

$$T_{3,2} = R_3 \left\{ \left[\frac{1 - \frac{(1-p_3)}{R_3} r_3}{1 - \frac{(1-p_2)}{R_2} r_2} \right] \left[C(\frac{1}{R_2} - 1) + \frac{T_2}{R_2} \right] - C(\frac{1}{R_3} - 1) \right\} \quad (12)*$$

Special case: $b_o H_o = b_2 H_2 = b_3 H_3 \equiv bH$ (i.e., $r_o = r_3 = 1$)

$$T_{3,2} = C \left(\frac{p_3 q_2 - p_2 q_3}{p_2 - q_2} \right) + T_2 \frac{p_3 - q_3}{p_2 - q_2} \quad (12a)*$$

(as reduced with the aid of considerable algebra)

13. Breakeven test cost, T_{Bi} , is defined as the cost of test i which yields $\overline{NB}_i = 0$, i.e. the test cost at which the increased costs incurred by testing, and then collecting and testing additional blood to replace the discarded blood, is exactly balanced by the savings resulting from the reduced health costs. Thus when $T_i = T_{Bi}$, from Eq. 9:

Total costs ₀ - Total costs _i = 0

After substituting Eq. 8 and solving for T_{Bi} :

$$T_{Bi} = C(R_i - 1) + Pb_0H_0[R_i - (1 - p_i)r_i] \quad (13)^*$$

Special case: $b_0H_0 = b_iH_i \equiv bH$

$$T_{Bi} = C(R_i - 1) + PbH[R_i - (1 - p_i)] \quad (13a)^*$$