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THE CLINICAL CONSEQUENCES OF PROTRACTED EXPOSURE TO FALLOUT

by

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The Clinical Consequences of Protracted

Exposure to Fallout

Fortunately for all, data concerning the effects of protracted exposure to fallout have not been made available since the publication of Report # 29 through the occurrence of catastrophes. In this presentation I shall attempt to assess those bits of human data that have accumulated during the past ten years in an attempt to determine if the basic clinical premises used in the planning for Report # 29 and their relation to radiation dose were far astray.

The large mass of data derived from animal studies simulating in some respects total doses and dose rates to be expected in the cases of fallout under emergency conditions are being discussed by my colleagues during this session. With the exception of one study to be discussed later the data concerning human effects do not resemble the actual fallout situation, but have the advantage that they were done on man and need not introduce

the further perturbation of the extrapolation to man of data derived from species other than man. During the past ten years there have become available several studies on the effects of single large doses of radiation to man carried out in the course of the treatment of malignant diseases and also as a means of suppressing the immune mechanisms preparatory to organ transplantation.

The studies of dose relationships to irradiation responses ranging from malaise and anorexia to death were carried out by Lushbaugh and colleagues (1) on 93 patients irradiated for therapeutic purposes in the Oak Ridge Institute for Nuclear Studies (ORINS) total-body irradiation facility and 7 nuclear radiation accident victims who were treated at the ORINS Medical Division. All of the ORINS patients had either an inoperable malignancy or a blood dyscrasia for which they have received previous conventional therapy and the disease process was in relapse at the time of their exposure. It must be noted, in an

analysis of the results, that only the seven men exposed in the radiation accident were normal; the others were suffering from otherwise lethal diseases. Eighty-four patients were exposed to 50, 100, or 300 R of ^{137}Cs gamma radiation at the rate of 0.75 to 1.6 R/min. The nine others were exposed to opposing-beam irradiation with ^{60}Co gamma radiation. The dose in R in air was converted to midline epigastric rads by using a conversion factor of 0.66. Seven quantal clinical responses were studied, namely, anorexia, nausea, vomiting, diarrhea, fatigue, listlessness, and death.

The resulting 100 midepigastric doses were found to be clustered in four groups of unequal numbers of cases. The arithmetic and geometric means of each group were used for the subsequent linear and logarithmic line-fitting programs. Probit analysis of Effective Doses (ED_{50}) using arithmetic dose yielded the following: for anorexia 82 ± 32 rads (S.E._m), nausea 130 ± 20 ,

vomiting 173 ± 18 , fatigue 136 ± 36 , diarrhea 194 ± 19 ,

and death 281 ± 44 . Of course, the clinical picture

in this series of studies could conceivably be colored

by signs and symptoms related to the patients' under-

lying diseases. In order to attempt to obviate

this possible perturbation Lushbaugh et al (2) extended

their studies by the addition of 63 more cases and

adjusted the patients' responses for the natural

incidence of the response using Abbott's formula.

The percentage of response due to natural incidence

was arbitrarily assumed to be the Y intercept (a) at

zero dose of the probit regression line fitted

linearly to the uncorrected data. On the basis of the

addition of the 63 cases the normal ED_{50} arithmetic

distribution for two end points, vomiting and death,

now become; vomiting uncorrected 198 ± 16 rads,

corrected 214 ± 22 rads or 325 ± 33 R; and death

uncorrected 243 ± 22 rads, corrected 251 ± 28 rads or 381 ± 43 R. The authors stated that "extrapolation from these data for estimation of higher probability levels of response (ED_{95}) must be restricted because these studies contain few observations at high dose levels. Our analysis appears to show that disease produces negative skewness in the apparent radiation dose-response relationship." The 95% confidence intervals for the quantal postirradiation response, death within 60 days based on the 100 case series and uncorrected yield a lower estimate of approximately 210 rads and an upper limit somewhat in excess of 400 rads. It would seem that on the basis of this careful study done on man no violence is done to the Report # 29 assumption of a 60 day LD_{50} for man in the domain of 450 R or 300 rads. Nor does the dose estimated to evoke the response, vomiting, seem to be astray.

An excellent summary of the effects of fractionation of radiation dose on skin effects, namely, erythema and moist desquamation, as well as a discussion of the relationship between total-body versus partial-body irradiation on haematologic effects is contained in the report of the Space Radiation Study Panel of the National Academy of Sciences--National Research Council (3). Although these discussions are germane to the problem at hand, I prefer to direct our attention to observations which more closely mimic the actual fallout situation of irradiation of man. Martinez and colleagues (4) have reported in detail the effects of continuous total-body irradiation of five members of a family who were unwittingly and for the most part continuously exposed to ^{60}Co gamma radiation.

The survivor of the exposure of five persons, a male aged 30 years was exposed over a period of 106 days to a radiation dose estimated to range between 984 and

1,716 rem, and received the smallest exposure in this incident. On the thirty-sixth day after initiation of exposure, which was at a dose rate which was estimated at between 9.3 rem/day to 16.2 rem/day, he developed fatigability and blackening of the nails of the fingers. One hundred and seventy-eight days after the onset of exposure the patient had a leukopenia of 2,200 cells/mm³ and a platelet count of 190,000/mm³. Four months later his leukocyte count was 5,400 and platelet count 190,000. The bone marrow biopsy done at the time of greatest peripheral blood cell depletion showed diminished cellularity and also diminished megakaryocytes. By the 204th day after the onset of exposure and 55 days after its cessation the bone marrow biopsy was reported as normal except for discrete "alterations in the megakaryocytes." If one were to attempt a correlation of the clinical and haematological picture with that seen in the acute total-body radiation accident cases reported

in the past, he would not be far afield if he estimated that this corresponded to a total acute dose of no more than 200 R or 130 rad. Certainly from the time course to death in two other of the cases in this accident and in the clinical picture leading to recovery in the previously described one, there is confirmatory evidence in man of recovery and of the mollifying influence of low dose rate.

In the past several years a vast amount of data have been gathered concerning the late effects of radioelements concentrated in the human skeleton and thyroid.

An extended discussion of these effects is in order at this time. In the studies carried out by Conard and his colleagues (5) eleven and twelve years after the fallout exposure of the inhabitants of Rongelap and Utirik Islands especial attention has been paid to the effects of the ingestion of fallout on the thyroid gland. The authors state that "in addition to the

^{131}I the isotopes ^{133}I , ^{135}I , and to a less extent ^{132}I

contributed significantly to the thyroid dose. The

only direct data on the Rongelap people are the radio-

chemical analyses of pooled urine samples taken 15 days

and longer after the fallout. Three separate estimates

have been made of the dose from the radioiodines to

the thyroid glands of adults exposed on Rongelap:

150 rads (from direct measurement of urinary ^{131}I), 100

rads (by indirect measurements on pigs removed from

Rongelap plus Marshallese urinary excretion data), and

160 rads (based on recent recalculations of early data).

On the basis of a consideration of the various differ-

ences in size of the thyroid, differences in turn-over

rates, and so forth, the radiation dose from the

various radioiodines to the thyroid of children less

than four years of age was estimated to be about 1000

rads, with a range of 700 to 1400. The glands of adults

and children received an additional 175 rads from external gamma radiation.

Until 1963 no thyroid abnormalities were detected in the exposed or control populations. However, beginning at 9 years after exposure a total of 18 cases of abnormalities of the thyroid have been detected. Nodules of the thyroid were found in 16 cases and 2 had hypothyroidism with growth retardation, but with no nodules. All occurred in the more heavily exposed Rongelap people except for one in the less exposed (Ailingnae) group. Of the 16 cases with nodules, 11 have had surgical procedures carried out on their thyroids. The glands for the most part demonstrated multiple adenomatous nodules and cysts. One patient, a 42-year-old female who was 30 years of age at the time of exposure, had a mixed papillary and follicular carcinoma of the thyroid with metastases to the regional lymph nodes. The authors state that it is

noteworthy that the preponderance of thyroid abnormalities have occurred in children exposed at less than 10 years of age and only in the more heavily exposed group (15 of 19 children, 78.9%). No cases with thyroid abnormalities were detected in the children in the lower exposure groups of the same age range from the other islands or in the 61 unexposed Rongelap children. Two adults with thyroid nodules were noted in the more heavily exposed Rongelap group and one in the Ailingnae group. In the Utirik and unexposed populations a low incidence of thyroid nodules was found, and these occurred only in the older age group.

Let us now turn our attention to a consideration of the state of knowledge concerning the late effects of the deposition of the bone-seeking radioelements in the skeleton of man. Until the present it has not been possible to relate the build-up of ^{90}Sr in the skeleton of man from weapons-testing or the past war time use of

nuclear weapons either with an increase in leukemia or with an increase in the incidence of malignant bone tumors to a level that could be sorted from the "natural incidence." However, a large mass of evidence and material has accumulated during the past 20 years in the United States and in other countries concerning the quantitation, excretion rates, and late effects of the deposition of ^{226}Ra in the skeleton of man. Three major projects have been under way in the United States and I shall describe the findings of my colleagues and myself at the Argonne National Laboratory and the Argonne Cancer Research Hospital in Chicago (6). This group of radium-bearing patients is composed of those persons who worked as radium dial painters in the State of Illinois in the 1914-1930 period, and a group of patients who had been administered radium orally or parenterally as a medication for a wide variety of diseases during the period approximately 1920-1933. The incidence of radium-induced malignant

tumors and blood dyscrasias was related to current or preterminal radium burden measurements for a series of 293 persons. The 46 malignant diseases observed included 23 bone sarcomas, 16 neoplasms of the skull (principally mastoid and paranasal sinus carcinomas), and 7 blood dyscrasias including leukemia. The current or preterminal body burdens of ^{226}Ra ranged from 0.60 microcuries to 10.70 microcuries. Another patient with a body burden of 0.13 microcuries had a peridental tumor thought by some to be a bona fide squamous cell carcinoma and by another to represent a tumor of the odontogenic apparatus of questionable malignancy.

Time does not permit a lengthy analysis of the intricacies of dose estimation to the bone and tissues sensitive to induction of tumors within the bone or immediately adjacent to it. However, as a gross approximation it can be noted that in a person bearing a 1 microcurie body burden of ^{226}Ra at 40 years after

the acquisition of the radionuclide the yearly radiation dose to the diffusely labeled bone will be of the order of 20 rads/year with a dose rate to the "hot-spots" or sites of concentration in certain Haversian systems of the order of 2000 rads/year. The cumulative rads for the skeleton as a whole will be in the domain of 2000-2500 rads in the previous 40 years.

The incidence of bone sarcomas uncorrected for age in our former dial painters is approximately 250 times the expected incidence in the United States for the year 1959. The incidence of tumors of the mastoids and paranasal sinuses approximates 450 times the expected incidence.

The large body of data which has been accumulated concerning the late effects of the one bone-seeking radioelement cannot easily be extrapolated to the fallout situation and ^{90}Sr . In a report published recently on behalf of the International Atomic Energy Agency and the World Health Organization (7) the discussion concerning

dose-response relationships states "The risk estimates in Table 1 are mainly based on information from radium in a few hundred individuals. It is not appropriate to extrapolate risk estimates, since the dose-response relationship is probably not linear." The report proceeds, "Radium and strontium absorbed into blood are eliminated from the body at different rates. From a comparison of time integral of internal contamination during a period 1 to 30 years after intake it can be estimated that 3 microcuries of ^{90}Sr at the end of 1 year give the same integrated exposure to bone as a terminal content of 1 microcurie of radium at the end of 30 years. Thus a terminal body burden of 1 microcurie of radium is considered equivalent in biological effect to 60 microcuries of ^{90}Sr in the skeleton one year after intake. It can be calculated that this corresponds to an intake of 1500 microcuries of ^{90}Sr by inhalation or 2000 microcuries

by ingestion." These statements, however, do not include estimates of the effect of early high dose rate on the oncogenic processes.

Let us now look at the data concerning body burdens of ^{90}Sr in the Marshallese. Conard and his colleagues state that in 1958, four years after the primary exposure, analyses of bone samples of one of the men who died showed a body burden of 3.7 nCi ^{90}Sr . "The mean level of urinary excretion of ^{90}Sr was 7.2 pCi/l or 14% higher than measured in the 1959 medical survey. In 1962 the mean urinary ^{90}Sr level was 114 pCi/g Ca, giving an estimated body burden of 12.0 nCi. Analysis of bones from the deceased Rongelap woman (1962) gave an estimated body burden of 11.4 nCi.

It thus appears that body burdens of ^{90}Sr have reached equilibrium with the environmental ^{90}Sr . Little or none of the present body burden of the exposed group can be considered residual from their initial exposure, since

little difference has been noted between the body burdens in exposed and unexposed populations living on Rongelap Island."

On the basis of the incomplete summary of human radiation effects which I have presented, what tentative conclusions can be drawn which bear on the clinical consequences of protracted exposure to fallout? First, no evidence has come to light which would lead me to assume that the 60 day LD₅₀ for man for an acute exposure to fission product gamma radiation is greater than 450 R or 300 rads, and it may be in the domain of 250 rads. The Mexican experience reinforces the evidence for man, well known for the experimental animal, of the presence of recovery and the mollifying effect of low dose rate. Parenthetically, the clinical picture demonstrated by the survivor in the Mexican experience is not a bad fit for an acute radiation dose in the domain of 200 R, which, if the estimates of total dose incurred are not

not far afield, fits closely the total protracted dose modified by the recovery rate factors used in Report

29. In addition, the fit is also good for an effective dose calculated by dividing the total absorbed protracted dose by the cube root of the time in days over which the dose was delivered.

Most disturbing is the evidence collected in the Marshall Island study of the especial radiosensitivity of the thyroid of the young. Although no malignant tumors have been seen in the thyroids of those exposed to the radioiodines from fallout when younger than 10 years, the degree of morphological alteration is striking, the incidence is probably 100%, the evidence for severe metabolic alterations in at least 2 of the children definite, and the disability severe. The true incidence of malignant thyroid tumors in the children attendant on this radiation dose will not be known because of thyroid surgery and the prophylactic administration of

l-thyroxine. We have, therefore, clear-cut evidence of severe thyroïdal disease ensuing from the ingestion of radioiodines falling out in a field which produced an acute external radiation dose of 175 rads. The late effects to the adult thyroid probably will not be seen for some time to come, although one thyroid carcinoma has already been observed and treated. The necessity for planning for thyroid blockade by various means to prevent or minimize the uptake of the radioiodines should be apparent to all.

What can be said concerning the hazards of the ingestion of ^{90}Sr during existence in a fallout field? As the pattern of dose-response relationships develops in the radium-bearing patients, and as the studies on the relative radiotoxicities of various bone-seekers in the large animal studies still under way become available, more precise estimates of risk may come to hand.

A critical gap in our knowledge is in the area of possible radiosensitivity of the skeleton of the child to tumor induction. Until this information becomes available, and it may never, our attention must be directed toward means of reducing and keeping to a practical minimum the ingestion by the child of the long-lived bone-seeking radioelements and ensuring that important nutritional elements are not at the same time removed from the diet by these remedial procedures.

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