Ann. Rev. Pharmacol. [illegible], 1973

TOXICOLOGY OF RADIONUCLIDES

6569

J. N. STANNARD[1]
University of Rochester, School of Medicine and Dentistry, Rochester, New York

TOXICOLOGY OF RADIONUCLIDES

On a weight basis many radionuclides must be viewed as among the most toxic agents known. For this reason and because of the potential of ionizing radiation to produce long-term effects both somatic and genetic, a very large amount of work has been done. In a sense our knowledge of these agents is almost out of proportion to the numbers of human beings affected directly, except for the ubiquitous exposure to nuclides from fall-out. For this reason the current tendency to put radiation hazards in perspective with other hazards, particularly in considering environmental pollution, is laudable (1). However, knowledge gained with radiation and radioisotopes is proving very useful to other areas of toxicology. Hence this review is directed primarily to the pharmacologist-toxicologist rather than to the specialist in radiation biology.

Radionuclide toxicology has not been covered in this Annual Review series since [illegible] of Catsch [illegible] 1963 (2). [illegible], a veritable flood of new work has been completed, much of it the result of experiments and programs begun [illegible] before. [illegible] of reviews, symposia, and monographs (3-17), but except for the monograph of Spiers (3), none appear [illegible]. A large compendium on [illegible], and the trans[illegible] elements (18), should be available at about the same time as this review and certain of its chapters are referenced specifically in these pages for [illegible].

Because of space limitations [illegible] be highly selective and frequently somewhat superficial. Some entire areas have been omitted (e.g., biochemical effects, instrumentation, nuclear medicine, therapy of radionuclide deposition), others given short shrift (e.g., "metabolic" patterns, fetus and newborn, inhalation [illegible] been described in more detail both because [illegible] better and [illegible] for Soviet and UK work, it is most extensive. Emphasis is placed on [illegible], dose-response relations and dosimetry, and environmental aspects of the general problem including references to the [illegible] during the last five years in each area [illegible] selection has been essential.

[1] This work was supported [illegible] to the Atomic Energy Commission at the Atomic Energy Project of the University of Rochester School of Medicine and Dentistry, Rochester, New York, and [illegible] assigned Report No. UR-3490-182.

General Considerations

The effects of radionuclides deposited in living cells, tissues, and organisms are considered to reside almost entirely in the ionizing radiation produced. With some nuclides of very low specific activity, e.g., natural uranium and thorium, chemical toxicity may play a significant role. Except incidentally, this is not pertinent here. There are a few very puzzling circumstances, e.g. the low carcinogenicity of radon gas in animals (19) compared to the high carcinogenicity of some other alpha-emitters after inhalation, which tempt introduction of a specific chemical effect for the more effective nuclide. Another example is that mentioned by Moskalev (6) concerning nuclides such as ^{60}Co, ^{59}Fe, ^{65}Zn, ^{35}S, ^{45}Ca, etc., which represent analogs of stable elements normally present in the biosphere.

Until the microdosimetry of radiation sources in tissue is so highly developed that there is no chance for discrepancies such as those mentioned to be accounted for by variations in the energy deposition pattern in time and space, radiation effects (including recoil and excitation energy) will be assumed to be sufficient except for low specific activities, presence of carrier, etc. Thus the chemical properties of the nuclide and its compounds enter primarily as determinants of sub-cellular, cellular, and tissue localization. These, in turn, control biological effects to a large extent by determining the distribution of radiation dose both microscopically and macroscopically. Toxicology of radionuclides, despite the commonality of ultimate effect with sources usually external to the body such as X, γ, and neutron radiation, is thus idiosyncratic.

Acute effects of deposited radionuclides are similar to the acute radiation syndrome (20) seen with external sources, particularly with nuclides that are not highly localized. All dividing cells, and therefore the tissues in which they reside, may be affected severely and the pathology is derived from their progressive malfunction. The long-term sequelae of moderate doses of greatest interest are carcinogenesis, genetic changes, and nontumorous forms of pathology including nephrosclerosis, pneumosclerosis, fibrosis; vascular pathology including hypertension; endocrine, and immunologic disturbances; transient and long-continuing hematopoietic disturbances; and nonspecific changes including life-span shortening, an effect that may be unrelated to specific pathological changes (21). As discussed later, the effects of very low doses usually must be inferred from these.

A good example of the broad range of effects seen after moderate doses of an effective soft-tissue seeker is in studies with ^{210}Po (8). This entire area has just been brought completely up to date and extensive USSR work added by [illegible] & Parfenov (22). The similarity of the effects to "radiation sickness" is emphasized particularly in this latter work.

Other recent full-range studies include a series of monographs on the toxicology of radioactive substances edited by Letavet & Kurlyandskaya (23). They cover in turn strontium, ruthenium, cesium, and radon (24); radioactive cobalt, sodium, phosphorous, and gold (25); iron (26), ^{232}thorium, and ^{238}uranium (27); and [illegible] living cells, tissues, and organisms [illegible] the ionizing radiation produced. With [illegible] e.g., natural uranium and thorium, [illegible] role. Except incidentally, this is not [illegible] the circumstances, e.g. the low carcino- [illegible] compared to the high carcinogenicity of [illegible], which tempt introduction of a [illegible] nuclide. Another example is that [illegible] nuclides such as ^{60}Co, ^{59}Fe, ^{65}Zn, ^{35}S, [illegible] elements normally present in the

[illegible] tissue is so highly developed [illegible] as those mentioned to be accounted [illegible] pattern in time and space, radiation [illegible] energy) will be assumed to be sufficient [illegible] of carrier, etc. Thus the chemical [illegible] enter primarily as determinants of [illegible]. These, in turn, control biological [illegible] the distribution of radiation dose both [illegible] toxicology of radionuclides, despite the [illegible] usually external to the body such as [illegible].

[illegible] are similar to the acute radiation [illegible], particularly with nuclides that are [illegible] and therefore the tissues in which they [illegible] is derived from their progres- [illegible] of moderate doses of greatest interest [illegible] numerous forms of pathology [illegible] fibrosis; vascular pathology includ- [illegible] disturbances; transient and long- [illegible] nonspecific changes including life- [illegible] related to specific pathological changes [illegible] low doses usually must be inferred

[illegible] effects seen after moderate doses of [illegible] ^{210}Po (8). This entire area has [illegible] extensive USSR work added by [illegible] to "radiation sickness" is

[illegible] monographs on the toxicology [illegible] (23). They cover [illegible], radioactive cobalt, sodium, [illegible] and ^{238}uranium (27): and

^{65}Zn (28). Each approaches the subject from the viewpoint of general pathology and general toxicology with multi-faceted studies. The volume on ^{65}Zn includes, for example, changes in the electric activity of the cerebral cortex of rabbits (29), effects on the functional state of the heart (30), serological changes (31), immuno- logy (32), some of which are hardly touched upon at all in work from laboratories in other parts of the world. We are, therefore, greatly indebted to G. W. Dolphin for his editing of the translations of these volumes into English.

CARCINOGENESIS

The most common, most feared, and most studied long-term toxicologic effect of deposited radionuclides is the induction of neoplasia. Ionizing radiation administered under the proper conditions seems to be nearly a universal carcinogen. In all forms, alpha and beta particles, photons, neutrons, accelerated particles, heavy nuclei, etc., cancer has been demonstrated to occur either in increased incidence or by temporal advancement of normal incidence with moderate to high doses. That it can occur at low doses is a reasonable extrapolation but subject to much controversy (see Dose-Response section).

None of these cancers are unique to ionizing radiation but can be caused by a variety of other agents, and there is growing interest in the role of promotional agents, i.e., co-carcinogens such as viral agents (33), and chemical agents (1, 34). Calvin (35) speculates that the three most studied modes of carcinogenesis—viral, chemical, and radiation—may have a molecular process in common, although final proof of this has not yet appeared.

That these processes may involve somatic mutations has been believed possible for at least two decades. Recent reconsideration of the phenomena of plutonium and radium toxicology on the theory of steady-state mutation rates (36) reasons the phenomena through on a general basis using absolute rate theory—a break-through from our all-too-common dependence on strictly observational approaches.

In the period covered by this paper, potential for carcinogenesis of a large variety of radionuclides has been reviewed and documented profusely (4–8, 13–18).

Carcinogenesis by Alpha Emitters

^{226}*Radium and related nuclides in man.*—The classic benchmark for the study of neoplasia induced in man by radionuclides is found in studies of dial painters, radium chemists, and patients receiving radium as a therapeutic nostrum. The important nuclides are ^{226}Ra (half-life 1620 yr), ^{228}Ra (Mesothorium, half-life 5.7 [illegible]) and [illegible] decay products. A definitive summary of the MIT studies [illegible] by Evans, Keane & Shanahan (37) as something of a valedic- [illegible] continuous work. Of a known population of over 22[illegible] [illegible] 1300 have been located and about 800 studied—[illegible] living [illegible] autopsy or exhumation cases and 120 unexposed matched living controls.

Radiological effects are seen at average cumulative skeletal doses above between 1000–1200 rads. The mean bone tumor occurrence (sarcomas and head carcinomas) among the epidemiologically suitable (unselected) high-dose cases is 0.28 ± 0.06. Incidence remained almost the same over a wide dosage range from 1000–20,000 cumulative rads. At lower doses (about 500 individuals) no radiogenic tumors or other discernable changes were found, i.e., there appears to be no clinically significant change below a residual body burden of about 0.5 uCi of pure ^{226}Ra. Also, no linear analytical function gives a close-fit to the dose-response relationship for tumor incidence. "Classical X-ray score", a numerical evaluation of all skeletal effects in each individual, did rise with dose, again with little significant change occurring below 1000 rads. The incidence of severe injury is greater with increasing cumulative dose, and the age distribution at death plunges markedly downward. Thus, it is only the tumor incidence that appears to have a "flat" dose-response relationship in the range 1000–20,000 cumulative rads.

In contrast to expectations from animal experiments with alpha emitters (38, 39) there seemed to be a dose-rate effect in these studies of alpha irradiation in humans (less change per cumulative rad-year at lower dose rates), although rather complex computations are required to demonstrate the effect.

Another human population studied independently at the Argonne National Laboratory and Argonne Cancer Research Hospital covers an identified group of about 525 persons of whom 293 have been studied in some detail. Most of these patients received "pure" ^{226}Ra iatrogenically. Finkel, Miller & Hasterlik (40) report [illegible] malignant disease in these 293 cases, 23 bone sarcomas, 16 carcinomas (mostly of mastoid and paranasal sinus), and 7 leukemias and aplastic anemias. [illegible] a comparable unexposed population. Dosage parameters were comparable to the MIT cases but without the complexity of the presence of short-lived isotopes in the source. For a variety of reasons these authors prefer to express dosage primarily as maximum radium burdens or current or preterminal burdens rather than as a calculated radiation dose in rads. Incidence of [illegible] malignant tumors rose more or less linearly with dose above 0.2 uCi ^{226}Ra (mean) current or preterminal burden or about 1.2 uCi ^{226}Ra (mean) estimated maximum burden. No cases were found below these mean values of body burden. Thus a possible threshold appears in these data also. If the same conventions of dosimetry calculation are used as applied by Evans and co-workers to the MIT cases, the applicable rad doses in the Argonne studies are reasonably comparable to those in the MIT study.

The reason there [illegible] to be a flat dose-response relation above the "critical" dose in the MIT cases but a more or less linear relation in the Argonne cases is not clear. It may [illegible] be a real difference. The data are presented in different [illegible] of the populations, particularly with regard to [illegible] various groups is not identical. [illegible] the populations are [illegible] in many respects. The difference may actually reside in the methods of data handling, a view strengthened, though not proven, by an analysis (41) of the combined MIT and ANL-ACRH cases. With 777

...currence (sarcomas and head carcino-
... (unselected) high-dose cases is 0.28 ±
... a wide dosage range from 1000-
... about 500 individuals) no radiogenic
... found, i.e., there appears to be no
... body burden of about 0.5 uCi of
... function gives a close-fit to the dose-
... classical X-ray score", a numerical
... individual, did rise with dose, again with
... rads. The incidence of severe
... dose, and the age distribution at
... only the tumor incidence that
... relationship in the range 1000-20,000

... experiments with alpha emitters
... these studies of alpha irradiation
... at lower dose rates), although
... to demonstrate the effect.
... independently at the Argonne National
... Hospital covers an identified group
... been studied in some detail. Most of
... Finkel, Miller & Hasterlik
... these 293 cases, 23 bone sarcomas, 16
... sinus, and 7 leukemias and aplastic
... comparable unexposed population.
... cases but without the complexity
... source. For a variety of reasons
... as maximum radium burdens
... as a calculated radiation dose in
... rose more or less linearly
... preterminal burden or about
... burden. No cases were found below
... possible threshold appears in these
... calculation are used as applied
... the applicable rad doses in the
... those in the MIT study.
... relation above the "critical"
... relation in the Argonne cases is
... The data are presented in
... particularly with regard to
... identical. Also, the popula-
... The difference may actually
... strengthened, though not proven,
... ANL-ACRH cases. With 777

dose-response expression in squared exponential form [$I = KD^2e^{-D/D_0}$, where I = incidence, D = total skeletal dose (mean) accumulated to the time of diagnosis]. When the analysis was repeated with later data by the same group (42) the carcinoma cases, now 20 of the 71, did not fit a continuous function over the entire dose range although the sarcoma data continued to fit the above function reasonably well.

The MIT and Argonne populations are in process of being combined for further study, concomitant with the official retirement of Dr. Evans from MIT. This and related problems are consolidated in a "Center for Radiobiology" in the Division of Radiological Physics at the Argonne Laboratory under the direction of Dr. Robert E. Rowland. Thus, this invaluable resource to the understanding of the toxicity of radionuclides in man will, it is greatly to be hoped, continue in a virtually "immortal" organization. Currently known exposees are expected to survive well beyond the year 2000 and, from an epidemiological standpoint, a complete study is essential.

Radium-224 (Thorium-X) in humans.—An entirely separate population for determination of the carcinogenic effects of deposited radium in man is a population of about 2000 German subjects who received, shortly after World War II, repeated injections of ^{224}Ra (Thorium-X, half-life 3.62 days). They received a nostrum called "Peteosthor" for intended treatment of ankylosing spondylitis, tuberculosis, and other disease on the initial recommendation of a country doctor. Spiess (43) first described the population: 1178 names known, 802 individuals checked, now 897 (44). Fifty-three bone sarcomas have now been reported with average time since the first injection standing at 21 years for juveniles and 18 years for the adults. Incidence seemed to be related more or less linearly to the average skeletal dose, with some inconsistencies. The incidence rate on this basis was 1.4% per 100 rads average skeletal dose for juveniles and 0.7% per 100 rads in adults. The lowest average skeletal dose associated with a bone sarcoma was 90 rads in an adult, about 120 rads in the combined juveniles. These minimal calculated doses (if they are minimal at all) are considerably below the comparable figures for radium-226 (1000–1200 rads). This may represent a greater inherent effectiveness of the shorter-lived radium isotope, but the difference is more likely to be a matter of dosimetric calculation. As Spiess & Mays point out (45), the calculated dose from ^{224}Ra to the cells at potential risk, e.g., in a soft tissue layer 10 μm thick adjacent to bone surfaces, is perhaps 9 times higher for ^{224}Ra than the calculated average to bone. The short-lived isotope expends much more of its energy while adhering to the bone surface than after incorporation into the mineral matrix. The result of a recalculation of dose on this basis ... raise the lowest sarcoma dose from ^{224}Ra and to reduce the ... for ^{226}Ra and almost eliminates the apparent difference in ...

... these results mean a real difference in effectiveness or a difference in dosimetric calculations, the fact that radiogenic tumors are occurring from radionuclide deposition in another human population is incontrovertible. Two leukemias have appeared in this population, but it is not certain whether they are radiogenic.

Of special interest in this study is the effect of protraction of exposure reported very recently (44). For a fixed total dose, observed incidence was higher on *protraction* of the exposure. This is contrary to the usual dose-rate effects seen in radiobiology which postulate that more recovery can occur at lower dose-rates and exceeds even the usual expectation of little effect of dose-rate with high linear energy transfer (LET) radiation (39, 46). Spiess & Mays offer several plausible radiobiological explanations for this unusual, but not unknown, effect of protraction, e.g., increased numbers of irradiated cells, less subsequent killing of premalignant cells, prolongation of the stimulus to cell division, etc. But it remains difficult to explain. A further examination of this phenomenon is clearly in order.

Uranium miners.—A third important human population demonstrating the carcinogenic effects of radionuclides is the group of miners who work underground in uranium mines. High incidence of pulmonary carcinoma occurs in this group. From a socio-economic standpoint, this is one of the most important exposed populations extant, as individuals are currently working and exposure control for them is a lively and immediate topic. But it is also a much more difficult group to analyze because of technical and scientific complexities—particularly dosimetry—than either of the radium groups.

The fact that miners in certain areas of Central Europe (Erz Mountains) had excessive disease of the respiratory system and that there was a high incidence of lung cancer has been known for a very long time. That it was due in part at least to exposure to radon (and its daughter products) in the mines is a much more recent realization (47). The most studied and analyzed population is the miners of the Colorado Plateau region in the United States. Several recent symposia and governmental reviews, including hearings before the Joint Committee on Atomic Energy of the Congress, provide ample documentation (48–[illegible]). The subject is still controversial but the primary facts have now been reasonably well settled.

The problem here is not uranium at all, but exposure to radon gas seeping into the tunnels from the decay of radium in the uranium ore to radon, and this in turn, decaying to its several daughter products, RaA (^{218}Po), RaB (^{214}Pb), RaC (^{214}Bi), RaC′ (^{214}Po), RaD (^{210}Pb), RaE (^{210}Bi), and RaF (^{210}Po). These latter may be present in varying proportions frequently attached to vector dusts, or they may develop in the body from cogenors that entered earlier. It is quite clear that the several daughter products are the principal offenders rather than radon itself. It is only the first four daughters that may exert their [illegible] effects as RaD (^{210}Pb) has a half-life of 21 years. Appreciable dose is not expected from the subsequent members, but they are of some importance toward retrospective determination of exposure. Since the biologically most important of these daughters are α-emitting nuclides, and all but radon

...population is ... overt...
...radiation, but it is not certain whether

...of protraction of exposure reported
...observed incidence was higher on
...to the usual dose-rate effects seen
...recovery can occur at lower dose-rates
...effect of dose-rate with high linear
...& Mays offer several plausible
...but not unknown, effect of
...irradiated cells, less subsequent killing
...stimulus to cell division, etc. But it
...of this phenomenon is clearly

...human population demonstrating the
...group of miners who work under-
...of pulmonary carcinoma occurs in
...point, this is one of the most important
...are currently working and exposure
...topic. But it is also a much more
...and scientific complexities—
...radium groups.
...of Central Europe (Erz Mountains)
...system and that there was a high incidence
...time. That it was due in part at
...products) in the mines is a much
...analyzed population is the
...United States. Several recent
...hearings before the Joint Com-
...ample documentation (48–50).
...facts have now been reasonably

...that exposure to radon gas seeping
...in the uranium ore to radon, and this
...products, RaA (^{218}Po), RaB (^{214}Pb),
...RaE (^{210}Bi), and RaF (^{210}Po).
...frequently attached to vector
...that entered earlier. It is
...the principal offenders rather
...that may exert their full radio-
...years. Appreciable dose in the
...but they are of some import-
...Since the biologically
...nuclides, and all but radon

itself are isotopes of polonium, the problem is, in part, a problem of the effects of the soft-tissue seeker, polonium (51).

Because of the difficulties of estimating body burdens in exposed individuals and bioassay in general, a measure of exposure was adopted that could be related to the radioactivity of the mine air. The unit agreed upon is the "Working Level" (WL), defined as any combination of short-lived daughters of radon (radium A, B, C, and C′) in one liter of air, which results in emission (not necessarily absorption) of 1.3×10^5 MeV of potential alpha energy in their decay to radium D. Integral exposure units are the "Working Level Month" (WLM) and the "Working Level Year" (WLY) and cumulative values of these (CWLM, CWLY). With certain assumptions regarding daughter-product ratios and percentage of free ions, 1 WLM is equivalent to about 7 rads (52) but with a large factor of variance, e.g., ± 5 rads.

While convenient to measure, these units have many problems. Radiation dose is not proportional to WL, WLM, or WLY, but depends upon the ratio of activities (concentrations) of the several daughter nuclides present and their clearance from the lung. Morken states (53), the factor may be as large as 9.6 between mixtures with only RaA and those with equal concentrations of RaA, RaB, and RaC. In a similar calculation, Pasternack (54) calculates a factor of 5 variation in the relationship of lung dose to WL (or WLM), depending upon the concentrations of RaA, RaB, and RaC present. It is only when there has been total decay of activity in the lungs, i.e., at the site of deposition, that the ratio of dose rate to working level is unity. Add the fact that dose to bronchiolar epithelium may be as much as a factor of 10 higher than average lung dose, and the WL is seen as a rather fluid measure of dose. Yet the short life of the daughters and their movement out of the lung make retrospective analysis of lung dose from excretion rates, deposition of ^{210}Pb or ^{210}Po almost as tricky. Therefore, the relatively measurable unit *in situ* has continued to hold sway.

In 1967 the Federal Radiation Council issued guidance for the control of radiation hazards in uranium mining (55). Because of the urgency of the subject, a NAS-NRC Advisory Committee prepared a further report analyzing scientific findings of pertinence (52). This report concluded that a causal association exists between lung cancer incidence in the mines and exposure to 1000 cumulative WLM (CWLM) or more, that there is a statistically significant increase in lung cancer risk for miners receiving between 100–400 CWLM, and that radiation exposure from radon daughter products contributed substantially to this increase. The increases in lower WLM groups were not statistically significant but may become so with time as more individuals enter the group under study. As a generalization, the number of lung cancer cases among the uranium miners in the period 1950–1968 is about 6 times that of nonminers.

The Public Health Service group reexamined all of the evidence and updated its earlier [illegible] page in 1971 (50). This was coordinated with, and followed by, an "Interagency Uranium Mining Review Group" convened to examine the evidence again and make recommendations regarding the control of mine atmospheres. This group included the several cognizant Federal agencies and the

NAS-NRC. Its conclusions (56, 57) modify the earlier ones slightly, but in essence confirm the increased cancer risk for miners in the 120–359 CWLM range. A modified position is taken on the role of cigarette smoking. As the miners tend to be ubiquitous and heavy smokers, it had been difficult to find a sufficient number of nonsmokers to "control" the data. However, in the Interagency Report, it is concluded that cigarette smoking does not account for the excess incidence of cancer.[2] Also, the Interagency group identified certain biases in earlier work that indicate that the exposure levels may have been overestimated. Thus, the 120–359 CWLM category may actually be lower.

The histological cell type of bronchiolar carcinoma in uranium miners has been reported to be markedly different from that in the general population (58). Small cell undifferentiated types of tumors (2A and 2B under the WHO classification scheme) predominate among uranium miners. To verify this an independent panel of pathologists reviewed the histologic material recently (59). With a few minor disagreements this panel confirmed the earlier relative predominance of small cell and undifferentiated cell types. This may or may not be specific to radiation exposure. Current examination of other hard rock miners, fluorspar miners, iron miners, coal miners, etc., indicates that many of these, too, show an excess of undifferentiated cell tumors. But neither are radon and its daughter products necessarily absent in these environments.

Animal studies in this field have provided support for, and extension of, the data on human exposees and puzzling contradictions to the human data. One contradiction has been the difficulty in producing bronchogenic carcinoma in animals by exposure to radon itself (19, also Morken, personal communication), although preneoplastic change is suspected. The induction of lung cancer by nuclides in the daughter product chain is not seriously doubted. Indeed, [illegible] Berke & Hull (60) show that ^{210}Po is a very effective agent in producing lung cancer in rats.

Stuart and others in the Battelle-Northwest group have been exposing hamsters and dogs to various mixtures of radon daughters, uranium ore dust, diesel exhaust fumes, and cigarette smoke (61–63). Early results (61) show bronchiolar hyperplasia but no significant differences among the groups as yet.

Kilibarda et al (64) found that radon (at 7.36×10^{-8} Ci/l) did not modify the development of silicotic nodules or otherwise significantly modify the histopathologic picture of rats receiving radon and SiO_2 simultaneously. This confirms earlier work by French authors. However, the time of observation was rather short.

A prolific literature has developed, much of it during the period of this review, on the deposition, translocation, and excretion of radon and its several daughter

[2] The reasons for this shift in view are not very clear. No large group of nonsmoking [illegible] miners has been added. However, expansion of the surveys to other types of miners with an equally high incidence of smoking may have contributed. This conclusion, however, must be viewed as somewhat tentative, since there is not general agreement concerning it.

... modify the earlier ones slightly, but in ... for miners in the 120–359 CWLM ... role of cigarette smoking. As the ... smokers, it had been difficult to find a ... the data. However, in the Inter- ... smoking does not account for the ... group identified certain biases ... levels may have been overestim- ... may actually be lower.

... carcinoma in uranium miners has been ... in the general population (58). ... and 2B under the WHO classifica- ... To verify this an independent ... recently (59). With a few ... the earlier relative predominance of ... may or may not be specific to ... other hard rock miners, fluorspar ... that many of these, too, show an ... that neither are radon and its daughter ... constituents.

... support for, and extension of, the ... to the human data. One ... bronchogenic carcinoma in ... personal communication), ... The induction of lung cancer by ... doubted. Indeed, Yuile, ... effective agent in producing lung

... group have been exposing ham- ... daughters, uranium ore dust, diesel ... Early results (61) show bronchiolar ... the groups as yet. ... (at 3.36×10^{-8} Ci/l) did not modify ... otherwise significantly modify the histo- ... and SiO_2 simultaneously. This confirms ... the time of observation was rather

... during the period of this review, ... of radon and its several daughter

... No large group of nonsmoking ... of the surveys to other types of ... have contributed. This conclusion, ... since there is not general agreement

products and the bearing of these phenomena on dose calculation. These include consideration of using the relatively longer-lived nuclides ^{210}Pb and ^{210}Po as measures of earlier exposure. This literature is documented in the several general reviews cited.

Thorotrast patients.—The fourth population of human exposees with primarily alpha-particle exposure contains a large but diffusely scattered group of patients who received thorotrast, a radioopaque medium used in diagnostic roentgenology, between 1930 and 1950. This colloidal preparation can remain *in situ* almost indefinitely. It contains several thorium isotopes in low but significant quantity, which wax and wane according to the age and treatment of the preparation. A variety of tumors of soft tissue, particularly of liver and the hematopoietic system, have been attributed to the presence of thorotrast (65). A sizeable population is potentially available for study particularly in Northern Europe, but also in Portugal, the United States, Japan, and elsewhere.

While there were earlier reports, a meeting sponsored by the International Atomic Energy Agency and WHO (66) provides a good collection of the cogent findings to that date. In some populations, e.g., Denmark (67, 68) the total incidence of tumors was not higher in the thorotrast patients but certain types of malignancies appeared that were rare in the control group. In others, e.g., Portugal (69) a notable feature was the excessive number of leukemias, while in Japan (70) increased incidence of both liver cancer and leukemia and shortening of the latent period appear to be associated with thorotrast depositions. However, the problems of radiation dose calculation, the low specific activity of thorotrast, and the relatively low incidence cast doubt on the interpretations except for the malignant vascular neoplasms that seem to be clearly associated with the exposures. Faber (67) recommends holding off for a much larger series of cases than any one has yet studied (10,000–20,000 vs 1000–3000 in the studied group) and an observation period of 25 years. Abbatt (71, 72) called for a coordinated international effort to reach these goals while the material was still available.

Dosimetry has been difficult, and even separation of radiation from chemical effects has caused concern for the validity of the results. The international effort urged in Vienna has not materialized. But a few further reports of effects have appeared.

Muth et al, in 1971 (73), summarized clinical examinations of thorotrast patients by groups in Homburg (Saar) and Frankfurt a. M. and correlated them with the total body burden of ^{208}Tl (ThC″), measured by whole body counting, and by thorium content of expired air. The new results do not provide a basis for either incidence or dose-response relationships of tumorigenesis. Of the 6000 patients whose records were analyzed, 70% are already deceased and measurement of body burden is not feasible, 18% cannot be located, while 12% have been measured and examined clinically. A high percentage of those with RES ... showed pathologic values in the Bromthalein test. Muth et al (73) reported only 3 patients with a primary liver tumor.

The results were more positive for chromosome aberrations in samples of peripheral blood. All of the 50 thorotrast patients examined showed abberations while none were seen in the control cases. Also a dose-effect relationship (stated to be nonlinear but in any event rising with body burden or calculated dose [illegible] appear possible to derive. The aberrations were largely breaks (5–80 per hundred scored cells) and dicentric chromosomes but not deletions or rings. The relationship between these findings and cancer incidence is, of course, still in the speculative stage.

It seems unlikely at the present juncture that the mammoth scientific and technical problems in the thorotrast patients will be solved in time to make this group as quantitatively satisfying as some of the others but it is hoped that the effort will continue nevertheless.

Plutonium.—There are no recorded incidents of cancer in man from the deposition of any plutonium isotope, although there have been some depositions in the worker population (74, 75). This reflects largely the effectiveness of control measures and perhaps also the relatively short time during which these low body burdens have been extant. Nevertheless, because of the importance of plutonium to the nuclear energy industry, full-scale animal studies have been underway since the early 1940s and have expanded considerably since the early and mid-1950s. Also there are metabolic data in man extending over many years. These have been reviewed, recalculated, and reinterpreted (76).

During the period of this review several milestones have been passed in the animal work. Dougherty & Mays (77) and Mays et al (4), report that the chief cause of death in their large beagle colony exposed to one of several bone-seeking radionuclides, ^{226}Ra, ^{239}Pu, ^{228}Ra (mesothorium), ^{228}Th, and ^{90}Sr is bone cancer. With ^{239}Pu, death with osteosarcoma 8 years after injection of plutonium appears to be about 6 times as likely (on an activity basis) as for ^{226}Ra. This high relative effectiveness is exceeded only by that for ^{228}Th.

The most recent data (78, 79) reconfirm this finding, and all studies reiterate in the dog the earliest suggestion of such a difference in toxicity between plutonium and radium made on the basis of work with rodents (80, 81). This empirical toxicity ratio has figured strongly in the setting of maximum allowable exposures to plutonium (75, 82).

The possible mechanisms for this difference have now been all but settled as residing in the mode of deposition of the nuclides in bone (4, 77, 81, 83, and many others). Plutonium deposits and remains on bone surfaces, whereas radium after a short period of surface attachment, exchanges with calcium and deposits more or less throughout bone mineral (although still not uniformly). This has led many to refer to plutonium as a "surface seeker" and to radium as a "volume seeker."

There are other differences. Plutonium deposits in soft tissue, while somewhat transiently, to a much greater extent than radium, and tumors of soft tissue, e.g. liver, are now appearing in animals carrying long-term deposits of plutonium (78). Bile duct and other lesions have also appeared. This has led Mays (84) to calculate the relative risk to bone versus liver cancer with parenterally injected

...cases. Also a dose-effect relationship (stated ... with body burden or calculated dose) did ...tions were largely breaks (5–86 per hundred ... but not deletions or rings. The relation- ... incidence is, of course, still in the specula-

...uncture that the mammoth scientific and ...patients will be solved in time to make this ... some of the others but it is hoped that the

...incidents of cancer in man from the deposi- ...ough there have been some depositions in ... reflects largely the effectiveness of control ...ively short time during which these low body ...es, because of the importance of plutonium ...-scale animal studies have been underway ...anded considerably since the early and mid- ...ta in man extending over many years. These ...and reinterpreted (76).

...several milestones have been passed in the ... and Mays et al (4), report that the chief ... colony exposed to one of several bone- ... ^{226}Ra (mesothorium), ^{228}Th, and ^{90}Sr is ...ith osteosarcoma 8 years after injection of ...es as likely (on an activity basis) as for ... is exceeded only by that for ^{228}Th. ...firm this finding, and all studies reiterate ...ch a difference in toxicity between pluto- ... work with rodents (80, 81). This empirical ...e setting of maximum allowable exposures

...difference have now been all but settled as ...nuclides in bone (4, 77, 81, 83, and many ...ts on bone surfaces, whereas radium, ...changes with calcium and deposits ...though still not uniformly). This has ...seeker" and to radium as a "volume

...its in soft tissue, while somewhat ...dium and tumors of soft tissue, e.g. ...long-term deposits of plutonium ...compared. This has led Mays (84) to ... liver cancer with parenterally injected

plutonium and to the conclusion that the risk is about equal but distribution depends on the route of entry. Hence the relative risk will also vary with the mode of administration and this conclusion cannot be extended to plutonium entering by routes other than injection.

The mean skeletal rad dose at the lowest level showing osteosarcoma to date is 78 rads at 1 year before death, 86 rads at the time of death and the years between injection and death: 9.92 (79). If we compare these to the numbers seen in other animals and men for ^{226}Ra the empirical toxicity ratio of slightly above 5 appears to be fully confirmed in this large experiment.

Recent work also makes possible comparison of the effective doses for osteosarcoma in rodents to those in beagles. Buldakov & Lyubchanskii (85) summarized work with 2208 rats receiving plutonium 239 at about 3 months of age. Incidence rates of about 3% are seen at average calculated skeletal doses of from 25–76 rads depending on route of entry and compound. Mays (personal communication) calculates the lifetime risk of bone sarcoma in this experiment as 0.06% per rad. But this may not be a smooth function, as many groups at low doses showed no osteosarcomas.

The data of Finkel & Biskis (86) using CF1 female mice show as calculated by Mays & Lloyd (79) 3.9% incidence at 40 rads dose accumulated up to 140 days before death. This is less than 0.1% incidence per rad. Neither of these rates are markedly different from those for the dog, e.g. 0.37% per rad at estimated start of tumor growth or perhaps lower. Since this figure is for monomeric plutonium (see page 336), which may be about twice as carcinogenic as the polymeric form, the difference among the species becomes even less significant. This relative confluence lends credence to extrapolation to man and the expectation that the carcinogenicity of plutonium in the bones of man may well be a factor of 5 or more greater than that of radium. This is the figure currently used in assaying hazards of man. Lloyd & Marshall (87) suggest that the relative effectiveness factor may be higher in man than in dog because of differences in bone structure and the higher rate of burial of surface deposits of ^{239}Pu in the dog.

The development of lung cancer in animals inhaling aerosols of plutonium has now been fully documented (19, 88, 89).

In an independent study on inhaled aerosols of ^{239}Pu and ^{238}Pu in the dog, Yuile, Gibb & Morrow (90) report increasing pulmonary pathology, typical of radiation effects, from about 1500–2000 rads to 15,000 rads. They do not, however, report frank pulmonary carcinoma.

Damage to accessory pulmonary structures, especially pulmonary lymph nodes, is commonly seen, especially if the compound inhaled is insoluble and is cleared from the lungs primarily by nonsolubilization processes. With plutonium oxide, major accumulations occur in tracheobronchial-lymph nodes: 50–100 times the concentration in lung. Fibrosis, scarring, and loss of lymphatic nodules are common, but frank neoplasia of these structures has not been found. Howard (91) reports that two dogs and several rats that inhaled "soluble" plutonium developed malignant lymphoma, and Lebel et al (92) report lymphoma in the regional lymph nodes of a dog receiving air-oxidized plutonium by subcutaneous injection. Lymphoma of the hepatic lymph nodes of a pig receiving plutonium nitrate subcutaneously is reported by McClanahan et al (93). Of special interest in the study of Yuile, Gibb & Morrow (90) is the fact that lung lesions seemed to reflect total pulmonary radiation dose while lymph node damage was more sensitive to dose rate.

Few "metabolic" studies of tissue distribution follow through the long-term toxicity to the extent seen in the work of Rosenthal & Lindenbaum (94). In this work plutonium received by intravenous injection in monomeric form was clearly more carcinogenic to bone (CF #1 female mice) than similar doses received in polymeric form. The mice receiving the monomeric form began dying earlier with osteosarcoma and developed about twice the incidence both in numbers of mice with tumors and in numbers of tumors per mouse. The higher concentration of monomeric plutonium upon endosteal surfaces of metaphyseal and vertebral trabeculae may have played an important role in this phenomenon, but it is difficult to arrive at a factor of 2 by this explanation alone. The polymeric plutonium deposits to a greater extent than monomeric in liver and other elements of the reticulo-endothelial system and incidence of hepatomas was 6% with the polymeric form compared to 2–3% with the monomeric plutonium. Whether or not this difference contributes also cannot be decided. Also the phenomenon may not occur to the same degree at very low concentrations of the nuclide.

The above may contrast with the findings of Della Rosa & Stannard (95) with ^{210}Po where large differences in tissue distribution did not influence acute toxicity. However the end points are quite different, *viz*: LD_{50} versus carcinogenicity.

All of the work quoted above refers to ^{239}Pu. Toxicity of ^{239}Pu has been reported as greater than ^{238}Pu on an activity basis (96) but the data do not extend to relative carcinogenicity.

Irradiated nuclear fuels always contain some americium-241 along with plutonium. For this reason comparative carcinogenicity of ^{241}Am to ^{239}Pu is of interest. Taylor & Bensted (97) have recently negated earlier findings showing equal toxicity of these two nuclides in a long-term study in rats. In their experiments ^{241}Am appears to be much less effective than ^{239}Pu in producing bone tumors: 21% and 47% incidence in animals receiving 2.5 uCi/kg or 7 uCi/kg of ^{241}Am respectively, compared to 80% incidence in animals receiving 2.9 uCi/kg of ^{239}Pu. The difference is attributed by the authors to differences in the chemical handling of the trivalent americium compared to the predominantly tetravalent plutonium, e.g. differences in binding to plasma proteins, clearance rate, etc. A few soft tissue lesions, including leukemia, were seen in this study but not in sufficient number to allow a comparison of effectiveness.

Even though no cancer cases or other serious lesions (except local deposit injury) have appeared in man, the population of plutonium workers is under constant surveillance (74). A United States Trans-Plutonium Registry has been organized under the sponsorship of AEC by the Hanford Environmental Health Foundation and all possible efforts are being made to study this group for com-

…lymph nodes of a pig receiving plutonium … McClanahan et al (93). Of special interest … is the fact that lung lesions seemed … while lymph node damage was more

… distribution follow through the long-term … of Rosenthal & Lindenbaum (94). In this … injection in monomeric form was … F … female mice) than similar doses … receiving the monomeric form began dying … about twice the incidence both in … numbers of tumors per mouse. The higher … upon endosteal surfaces of metaphyseal … important role in this phenomenon. … of 2 by this explanation alone. The poly… extent than monomeric in liver and other … and incidence of hepatomas was 6% … 2.3% with the monomeric plutonium. … attributes also cannot be decided. Also the … same degree at very low concentrations of

… findings of Della Rosa & Stannard (95) with … distribution did not influence acute … quite different, *viz*: LD_{50} versus carcino…

… to ^{239}Pu. Toxicity of ^{239}Pu has been … activity basis (96) but the data do not

… some americium-241 along with … carcinogenicity of ^{241}Am to ^{239}Pu … have recently negated earlier findings … in a long-term study in rats. In their … less effective than ^{239}Pu in producing … in animals receiving 2.5 uCi/kg or … to 80% incidence in animals receiving … attributed by the authors to differences … americium compared to the predomi… … in binding to plasma proteins. … including leukemia, were seen in … a comparison of effectiveness. … lesions (except local deposi… … plutonium workers is under … Plutonium Registry has been … Hanford Environmental Health … to study this group for com…

… lesion, and one melanoma of the chest has been reported in another individual, but correlation with plutonium deposition is very circumstantial at this juncture.

Natural Uranium.—Natural uranium (^{238}U plus small amounts of ^{235}U and ^{234}U) has been the subject of several long-term studies over more than two decades. These are now essentially complete. The effects of U-nat in soluble form are seen largely as nephrotoxicity and are attributed to chemical rather than to radiation effects. In insoluble form the effects of natural uranium are considered to be due to radiation, but only recently have neoplastic changes been demonstrated with this very low specific activity substance. After up to 5 years of exposure to UO_2 dust by inhalation at 5 mg U nat/m^3 on a 5-day per week schedule and a post-exposure observation period of up to 6.5 years the long-term Rochester experiment (98) has now shown pulmonary neoplasia in 4 of 13 exposed dogs and epithelial proliferation and metaplasia in several others. While this is a definite finding it is somewhat tempered by the fact that 25 exposed monkeys in the same experiment have shown only extensive fibrosis and no neoplasia as yet. It can be concluded that natural uranium is clearly not very likely to produce radiogenic tumors. Conversely, the fact that no kidney damage was seen by any measure, histological or functional, supports the conclusion that "insoluble" natural uranium is not likely to show nephrotoxic effects and its control should be based on potential radiation damage.

However even a change to uranium trioxide makes a large difference in pharmacokinetics and thus potential effects as demonstrated by Morrow, Gibb & Beiter (99). Hence any such generalizations should not be extrapolated unduly.

Carcinogenesis by Beta and Beta-Gamma Emitters

In general, nuclides whose carcinogenic action resides primarily in emission of beta particles and/or a gamma photon are less effective as carcinogens per rad than the alpha partile emitters. This seems to be true in part for other biological end points also. Recent work of special interest is summarized in this section.

Strontium and related nuclides in animals.—The concern generated by the presence in the biosphere of fission products from testing of nuclear weapons in the atmosphere led to massive experimental studies of the behavior and effects of these nuclides. While much work is still in progress many recent reports may be regarded as milestones. The published proceedings of a symposium on radiostrontium exposure held in Davis, California in February 197… are now available (1…) and bring up-to-date many aspects of this large field.

Thirteen … experiments are presented in the radiostrontium symposium. Neoplastic change is the primary end point and cause of death in 9 of these … rabbit and dog teratology is the principal effect in 1 study … and chromosome changes in man in 1 (102).

… clearly induced in dogs by injected radiostrontium (103–105), confirming earlier work with rodents. The tumors attributable to the ^{90}Sr-Y are osteosarcoma, hemangiosarcoma, and fibrosarcoma in bone as well as epidermoid carcinoma of the oral and nasal cavities, lymphosarcoma, myeloid leukemia, and reticulum cell sarcoma. There were some hematological fatalities in the Utah experiments.

Ingested ^{90}Sr has been associated with leukemogenic effects on bone marrow and the lymphoreticular system of miniature swine as described by Clarke et al (106) while Pool et al (107) report a high incidence of bone sarcoma in beagles receiving quite large radiation doses from ^{90}Sr received by ingestion.

McClellan & Jones (108) have summarized cogently much of the information on tumor incidence with radiostrontium in animals. Although small changes in the picture have occurred in the interim, their Table 10 is such a useful summary that it is reproduced below (Table 1).

Our experience with inhaled strontium (109) shows also a predominence of tumors of bone similar to the Utah and Argonne National Laboratory studies with dogs receiving single intravenous injections. This indicates that the inhaled strontium compounds are relatively more mobile than some of the insoluble oxides such as PuO_2 and that bone is apt to be the chief tissue at risk with strontium, regardless of route of entry, as long as the doses are small.

All of these studies show strontium to be considerably less effective as a carcinogen in bone than radium and the other alpha emitters. Its effectiveness relative to radium in the beagle experiment at Utah is about 0.07–0.24, and similar effectiveness ratios can be calculated from the other experiments.

In dogs inhaling $^{90}SrCl_2$, calculated cumulative doses associated with neoplasms ranged from 4000 rads to as high as 22,000 rads (110) compared to much smaller doses associated with similar degrees of development of bone sarcoma with radium, plutonium, and other alpha emitters. The new experiments confirm the greater effect of dose rate on carcinogenesis by beta and beta gamma emitters than by alpha emitters.

Human exposures to strontium isotopes.—Except for the worldwide population exposed to fall-out, to be discussed separately, there is only one discrete population of humans available for epidemiological study which has had exposure to radiostrontium. For a short period luminous dial painters in Czechoslovakia and Switzerland used a compound containing ^{90}Sr and ^{226}Ra. Volf (102) reports on a group of 163 cases. Müller and contributors (111] report on a group of 65 cases in Moravia and Saxony. In the first group, while chromosome abnormalities were about double the control rate and positive clinical findings appeared, no neoplasms occurred that could be attributed to the radionuclide exposure. Bone pains were, however, rather common. There were only 4 cases that were close to or exceeded the maximum permissible body burden for ^{90}Sr and ^{226}Ra [illegible] exposure.

In the report of Müller et al, karyotic changes were seen in every exposed individual, and a large portion of their study is devoted to analysis of this feature and to [illegible] kinetic studies. They do report 6 cases of carcinoma with incidence in an untreated group so low that the probability of seeing these

…, and fibrosarcoma in bone as well as … nasal cavities, lymphosarcoma, myeloid … There were some hematological fatalities

… with leukemogenic effects on bone marrow … miniature swine as described by Clarke et al … high incidence of bone sarcoma in beagles … from ^{90}Sr received by ingestion.

… summarized cogently much of the information … in animals. Although small changes in … their Table 10 is such a useful summary

… (109) shows also a predominence of … Argonne National Laboratory studies … injections. This indicates that the inhaled … more mobile than some of the insoluble … is apt to be the chief tissue at risk with … as long as the doses are small.

… to be considerably less effective as a car… the other alpha emitters. Its effectiveness … experiment at Utah is about 0.07–0.24, and … calculated from the other experiments.

… cumulative doses associated with neo… high as 22,000 rads (110) compared to much … degrees of development of bone sarcoma … alpha emitters. The new experiments con… carcinogenesis by beta and beta gamma

…topes.—Except for the worldwide popula… separately, there is only one discrete … epidemiological study which has had expo… luminous dial painters in Czecho… compound containing ^{90}Sr and ^{226}Ra. Volf … Müller and contributors (111) report on … In the first group, while chromosome … control rate and positive clinical findings … could be attributed to the radionuclide … rather common. There were only 4 cases … permissible body burden for …

… changes were seen in every exposed … study is devoted to analysis of this … They do report 6 cases of carcinoma … low that the probability of seeing these

TABLE 1.[a] **Effects noted in several species with administration of ^{90}Sr in different exposure patterns**

Exposure pattern	Route of Administration	Animal	Increased incidence of: Osteosarcoma	Hematopoietic neoplasms	Vascular neoplasms	Epithelial neoplasms	Earlier appearance of hematopoietic neoplasms
Single dose	IV	Mouse	Yes	Yes	Yes	Yes	Yes
	IP	Mouse	Yes	Yes	Yes		Yes
	IP	Mouse	Yes	No	Yes	Yes	
	IV	Mouse	Yes	Yes			
	Inhalation	Rat	Yes	Yes			Yes
	IV	Dog	Yes	No	Yes	Yes	
	IV	Dog	Yes	No		Yes	
	IV and IP	Rabbit	Yes	No		Yes	
Multiple doses over a short time period	IV	Mouse	Yes	Yes			Yes
	Oral	Rat	Yes	Yes		Yes	
	Oral	Monkey	Yes	Yes			
Multiple doses over a long period of time	Oral	Mouse	Yes	?		Yes	Yes
	Oral	Rabbit	Yes	No			
	Sub-Q	Dog	Yes	Yes			
	Oral	Dog	Yes	Yes			Yes
	Oral	Pig	Yes	Yes			Yes

[a] Table 10 from reference 4 page 313 reproduced (without author column) with permission of authors, editors, and publishe…

6 cases of malignant disease is only 0.0006. Yet the body burdens of all isotopes, ^{137}Cs, Radium C, and radon as well as ^{90}Sr–^{90}Y are so low [illegible] maximum permissible body burden for occupational exposure) that [illegible] refuse to believe the carcinomas to be radiogenic. They suggest a longer [illegible] of follow-up and further analysis of the group, before concluding that this is true incidence due to radiostrentium exposure.

Although the groups are complicated by the presence of radium isotopes [illegible] the paint and in the body burden, further analysis is important since the [illegible] Sr-[illegible] burdens are generally considerably greater than those of radium or [illegible] and effects, if they do appear, might thus be relatable to radiostrontium exposure.

Radioiodine.—The fact that radioiodine, primarily ^{131}I, can produce [illegible] carcinoma in animals is well-established. That ionizing radiation can and [illegible] produced thyroid neoplasia in man is also clear (112). Primary interest for [illegible] review centers on the populations exposed to fall-out and patients receiving radioiodine for the treatment of thyroid diseases. The fall-out exposures are considered under a separate heading. In the studies with patients, ^{131}I seems considerably less prone to produce thyroid carcinoma than comparable rad doses of external radiation by a factor of about 10.

Other iodine isotopes ^{132}I, ^{133}I, and ^{135}I seem to be more effective in producing thyroid carcinoma, and calculated doses are more similar to external radiation. Casarett (113) speculates that this difference may be due to the extremely nonuniform distribution of iodine isotopes in follicular colloid along with the relatively low energy of the ^{131}I beta particle compared to the other iodine isotopes.

A general estimate of the risk of thyroid carcinoma in children for external forms of ionizing radiation (largely X-irradiation and gamma photons) is 10–20 additional cases per rad per million exposed persons (114). The risk from ^{131}I would thus be about 1–2 additional cases per rad per million in children and less in adults. Estimates for leukemia incidence from X-irradiation are about 20 additional cases per rad per million exposees.

In view of the greater mortality from leukemia than from thyroid carcinoma, much concern has been expressed over the chances for leukemia induction from radioiodine in the treatment of thyrotoxicosis. This has received more emphasis recently than the induction of thyroid carcinoma. In 1968 Saenger, Thoma & Tompkins (115) published a preliminary report on a group of 36,000 patients (with 98.8% follow-up) which indicated that there was no difference in leukemia incidence between patients receiving ^{131}I or thyroid surgery. But with either treatment the observed mortality from leukemia for hyperthyroid patients [illegible] group was reported as 50% higher than for the general U.S. population. Tompkins followed this preliminary report with a more detailed study in 1970 [illegible] The age-adjusted leukemia incidence rate was 11 per 100,000 patient years in the ^{131}I—treated patients and 14 in those treated by thyroidectomy. Thus the lack of a gross increase was confirmed, although the converse effect was not confirmed, as a much larger population would have been needed to prove this.

... 0.0006. Yet the body burdens of all isotopes ... well as $^{90}Sr-^{90}Y$ are so low (well below ... occupational exposure) that the author ... radiogenic. They suggest a longer period ... the group, before concluding that this is a ... exposure.

... cated by the presence of radium isotopes in ... ther analysis is important since the $^{90}Sr-^{90}Y$ ... greater than those of radium or cesium, ... as be relatable to radiostrontium exposure.

... iodine, primarily ^{131}I, can produce thyroid ... shed. That ionizing radiation can and has ... is also clear (112). Primary interest for this ... exposed to fall-out and patients receiving ... thyroid diseases. The fall-out exposures are ... In the studies with patients, ^{131}I seems ... uce thyroid carcinoma than comparable rad ... factor of about 10.

... and ^{135}I seem to be more effective in pro- ... lculated doses are more similar to external ... that this difference may be due to the ... of iodine isotopes in follicular colloid along ... the ^{131}I beta particle compared to the other

... thyroid carcinoma in children for external ... X-irradiation and gamma photons) is 10–20 ... exposed persons (114). The risk from ^{131}I ... cases per rad per million in children and ... incidence from X-irradiation are about ... exposees.

... leukemia than from thyroid carcinoma, ... ever the chances for leukemia induction from ... rotoxicosis. This has received more emphasis ... carcinoma. In 1968 Saenger, Thoma & ... report on a group of 36,000 patients ... that there was no difference in leukemia ... ^{131}I or thyroid surgery. But with either ... leukemia for hyperthyroid patients as a ... the general U.S. population ... a more detailed study ... would have been ...

There was an apparent excess of acute leukemia in males receiving ^{131}I (5 cases observed versus 2.5 expected) and a comparable deficit in both sexes in incidence of chronic lymphocytic leukemia (2.0 observed versus 4.8 expected). These findings are compared to and found consistent with the data from the ankylosing spondylitics and atomic bomb survivors. Tompkins concludes that none of the studies demonstrate induction of leukemia at low total-body doses of irradiation and that ^{131}I treatment of thyroid disease carries no greater risk of leukemia than does surgery.

Induction of chromosomal aberrations by iodine-isotopes has ben reported in both animals (117, 118) and man (119).

Much of the information on iodine-isotopes in animals utilizes relatively high concentrations. Recently Thomas, Scott & Chiffelle (120) have reported on the metabolism and toxicity of inhaled and injected ^{131}I not only at moderately high dose levels but at levels considered in the past as "control" or "tracer". The average infinite beta radiation doses to the thyroids of these animals ranged from 797–4510 rads. The lowest infinite dose was 286 rads and the highest 18,600 rads. Thyroid tumors, usually follicular adenomas, occurred in all animals including the controls, but tumor incidence in the higher level animals was greater by a factor of about 3 over that in the control and low-level groups. There were also alterations in the pituitary gland with pituitary adenoma occurring after moderately high dosage. It is interesting to note that there was no alteration in life-span in animals maintained for a longevity study even though some of them received accumulative radiation doses to the thyroid of approximately 15,000 rads. However, biological change of a greater or lesser degree was seen at all of the dose levels.

Other beta and beta-gamma emitters.—Bair (19) summarizes the incidence of lung cancer after ^{144}Ce given by intratracheal injection, ^{106}Ru, ^{106}Rh pellet implants, ^{32}P implants, ^{60}Co wire implants, ^{198}Au, ^{59}Fe, ^{35}S, and ^{103}Ru after inhalation or injection. Sanders, Thompson & Bair (121) give an experiment-by-experiment review. Radiation doses to the lung are so high in all these instances that it is reasonable to conclude that these nuclides are relatively inefficient carcinogenic agents. However the studies do not ordinarily include many low-dose segments or sufficient time really to determine the long-term potentialities of these nuclides. There is a report of four squamous cell carcinomas (122) in rats inhaling ^{144}Ce oxide in amounts producing lung doses of only up to 2500 rads, and a large study with dogs receiving ^{144}Ce incorporated into fused clay is in progress at the Lovelace Foundation. Berke & Dettrich (123) find more pulmonary pathology than neoplastic change in rats receiving aerosols of [illegible] promethium 152–154.

[illegible] AND DOSE-RESPONSE RELATIONSHIPS

[illegible] dosage parameters for radionuclides are much more complex than in the ordinary practice of pharmacology or toxicology. This arises in large part from the proclivity of radiation biologists not to be satisfied with such simple parameters as administered dose. Since the units for dose of external radi... are in physical terms it is natural to try to present doses associated with effects of radionuclides in similar terms (i.e., rads and rems). Since the absorb... dose depends heavily upon the kinetics of absorption, distribution, retention, translocation, etc., at all levels of organization from organ systems to ce... much of the literature pertinent to the toxicology of radionuclides is devo... primarily to this aspect, i.e., pharmacokinetics. Space prevents any serio... consideration of this enormous literature here. Also in the practice of nucle... medicine it is desirable to know within reasonable limits the radiation dose ... the target tissue and others, either to prevent undue exposure in diagnos... tests or to deliver a known dose for therapy.

The classic schema for internal dose computation devised largely by Marinelli, Quimby & Hine (124) and universally applied since the late 194..., has be... expanded in the intervening years (125). Rather elaborate equations hav... developed for photons, beta particles, point sources, surface and volume sou... etc. As described by Loevinger (126) a simpler, more general treatment ... desired, particularly for the practice of nuclear medicine. To accomplish this group known as the "Medical Internal Radiation Dose Committee" (MIRD... was organized by the Society of Nuclear Medicine. Several pamphlets hav... been published as supplements to the Journal of Nuclear Medicine (127–13... which detail the work of this committee and its sponsors. They present as unifying principle the concept of "specific absorbed fraction" ($\Phi = \phi/m$ whe... $\phi =$ the absorbed fraction in mass m) which had been introduced earlier i... gamma-ray dosimetry (131). The pamphlets give the schema, tables of absorb... doses, radionuclide decay schemes, and other needed information. Futu... issues will concentrate on specific substances of interest in nuclear medicin... especially radiopharmaceuticals.

The principal accomplishment of the MIRD schema is to provide a sing... expression which covers dose from any source of activity to any target for ... types of radiation. It is stated to have general applicability as long as relev... geometric relations do not change with time (126). This latter is a not inconsid... able reservation with certain isotopes. But to the extent that absorbed fract... and specific absorbed fraction are parameters of interest for predicting biologi... effect, and to the extent the schema give them directly, the new plan has adv... tages. For those brought up with the Marinelli, Quimby & Hine method, ... new approach will seem unfamiliar and not an obvious simplification bu... may become clearer with use. Fortunately the absorbed doses calculated ... MIRD Schema are stated not to be radically different from those calcula... by the older methods (126, p. 487).

An equally important function of the MIRD committee is the ... of metabolic data and lifetimes of nuclides administered as ... pharma... ceuticals, along with information on factors such as chemical and ... purity, stability, etc. which might affect absorbed dose.

Greenfield & Lane (125) have contributed a timely and complete chapter ... radioisotope dosimetry aimed at both the researcher and the physician

Since the units for dose of external radiation ... to try to present doses associated with the ... terms (i.e., rads and rems). Since the absorbed ... kinetics of absorption, distribution, retention ... organization from organ systems to cells, ... to the toxicology of radionuclides is devoted ... pharmacokinetics. Space prevents any serious ... literature here. Also in the practice of nuclear ... within reasonable limits the radiation dose to ... to prevent undue exposure in diagnostic ... therapy.

... computation devised largely by Marinelli, ... generally applied since the late 1940s, has been ... (125). Rather elaborate equations have ... point sources, surface and volume sources, ... (126) a simpler, more general treatment was ... of nuclear medicine. To accomplish this a ... Internal Radiation Dose Committee" (MIRD) ... Nuclear Medicine. Several pamphlets have ... the Journal of Nuclear Medicine (127–130) ... committee and its sponsors. They present as a ... "specific absorbed fraction" ($\Phi = \phi/m$ where ... m) which had been introduced earlier for ... pamphlets give the schema, tables of absorbed ... and other needed information. Future ... substances of interest in nuclear medicine,

... the MIRD schema is to provide a single ... any source of activity to any target for all ... have general applicability as long as relevant ... time (126). This latter is a not inconsider- ... But to the extent that absorbed fraction ... parameters of interest for predicting biological ... give them directly, the new plan has advan- ... the Marinelli, Quimby & Hine methods, the ... not an obvious simplification but it ... the absorbed doses calculated by ... radically different from those calculated

... MIRD committee is the compilation ... administered as labelled pharma- ... such as chemical and radiochemical ... absorbed dose.

... a timely and complete chapter on ... both the researcher and the physician. It

"reflects the deliberations, if not the methods, of calculating absorbed dose" (125, p. 101) of MIRD but on the whole provides a somewhat more classical format. Also, a good survey of the "classical" approach can be found in the chapter by Harper (132) and the book by Hendee (133).

Hundreds of papers have addressed dosimetric problems of a particular isotope in a particular system. These cannot be reviewed here except in connection with dose-response relationships as a general problem. Of special interest, however, is a series of papers from the New York University Institute of Environmental Medicine by Wrenn and colleagues (134–136), on the radiation dose from nuclides that decay by electron capture or internal conversion. It is pointed out that frequently Auger electron emission, which can occur in such cases, is "more probable than x-ray emission for elements of biological interest" (134, p. i). The range of an Auger electron is considerably shorter than the mean free path of the equivalent x-ray. Therefore conventional dosage calculations may be quite inaccurate if the biological object of importance is small compared to the mean free path of the anticipated x-ray. If specific localization of an Auger electron emitter occurs in sub-cellular structures, very localized irradiation may take place. Conventional dosimetric calculations assuming uniform distribution would miss this almost entirely.

Wrenn (134) showed that the difference in dose to the erythrocyte with Fe-55 is a factor of 10 higher than to the rest of blood because of these phenomena, and with some iron-containing complexes such as ferritin which bind closely to intra-cellular structures, the difference between local dose and a conventionally calculated one may be even greater. Feige et al (137) and Gillespie et al (138) have explored the physical dosimetry in thyroid for ^{125}I, another Auger electron "emitter."

Dose-effect relationships.—Understanding and formulating the relationship of dose to effect is especially important in considering the effects of radionuclides at this time because of the strong current emphasis on the effects of very low doses. Acute effects at high doses of both external radiation and internal emitters generally follow the sigmoid relationship familiar in chemical toxicology. But genetic effects of radiation are characteristically linearly related to dose with no apparent threshold [with a recent exception—female mice (139)] and the same relationship is postulated to hold for some somatic effects including carcinogenesis. This has been termed the "linear no-threshold model." The 1972 paper of Evans, Keane & Shanahan (37) presents a useful history of this concept as applied to radiation protection, where it was adopted primarily because it was conservative (114, 140). That it gives an upper limit to risk is evident to the extent that the true relationship lies below a linear extrapolation from doses for which data are extant.

Evans et al have taken the view that the region of no-effect described in the section on carcinogenesis above is tantamount to a "practical threshold" in that the incidence is so low within the life span of the species concerned as to be negligible. Others (141–145) do not accept this view and maintain in essence that the linear no-threshold model can neither be supported nor refuted within much larger numbers of exposees in the low dose domain. A full-blown controversy has reigned over this matter and will probably not be settled to everyones satisfaction until studies now in progress or planned can be completed.

The animal experiments can contribute significantly, and show clearly that the answer is not a simple one. Mays & Lloyd (110) summarize 5 extensive experiments involving graded doses of radiostrontium and radiocalcium in mice, rats, pigs, and dogs. A linear relation does not fit the dose-response relation very well in any of them and at low doses there is always a lower incidence (frequently zero) than predicted by a linear extrapolation with no threshold. A sigmoid type relation fits better. By contrast, the analysis by Mays et al (79) of similar experiments with alpha emitters (plutonium, radium, etc.) shows a better fit to a linear no-threshold relation than to a sigmoid one. Tamplin & Gofman (143) insist that the linear hypothesis is the only one that fits the beagle-dog data for alpha emitters. If there is really a difference between the alpha and beta or beta-gamma emitters, as Mays' analysis suggests, the direction is consistent with known differences in cell and tissue recovery from effects of the two kinds of radiation, although other explanations may be just as valid.

An example of how risk estimates differ with the model is seen in the analysis of Mays & Lloyd. At doses below 1000 rads the projected risk (in man) in 50 years is 1 ± 1 sarcomas/10^6 person-rads for a "low-dose linear model" and 4 ± 4 sarcomas/10^{10} person-rads for a dose squared model. Thus the difference is not trivial!

Other models have been presented. Rosenblatt (146, 147) utilizes a three dimensional surface logistic model to account for simultaneous contribution of dose and time on osteosarcoma incidence in beagles receiving radium or radiostrontium, and employs the Cutler-Ederer life table method (148) in treating deaths from causes other than the one at issue. This logistic type response is not linear anywhere. Also, it permits age-related incidences to be calculated (e.g., 10% cumulative osteosarcoma incidence would occur at age 50 in the beagle). It is discussed in detail along with risk evaluations based on it by Goldman & Bustad (149).

Mole (150) describes the probability of bone tumor in mouse and dog receiving ^{90}Sr as directly proportional to the square of the number of beta particles emitted in the skeleton per kilogram body weight. This did not appear to hold, however, for alpha emitters. He also generalizes that the data from mouse, rabbit, rat, and dog demonstrate essentially equal radiosensitivity of the critical tissue (endosteal cells), a somewhat unexpected phenomenon.

Finally, as remarked by Evans et al (37) the linear nonthreshold model predicts the same number of injured individuals per person-rad regardless of how the exposure dose is subdivided in the exposed group. This has not in general been found for the somatic effects of radiation although it is generally assumed to be true for genetic effects. It almost never appears in chemical toxicology.

It must be obvious from all this that none of the studies, man or animal [illegible]ean neither be supported nor refuted without [illegible] the low dose domain. A full-blown con[illegible] and will probably not be settled to every[illegible] progress or planned can be completed.

[illegible]ribute significantly, and show clearly that [illegible]ays & Lloyd (110) summarize 5 extensive [illegible] of radiostrontium and radiocalcium in [illegible] relation does not fit the dose-response [illegible] at low doses there is always a lower incidence [illegible] a linear extrapolation with no threshold. A [illegible] contrast, the analysis by Mays et al (79) of [illegible]ers (plutonium, radium, etc.) shows a better [illegible] than to a sigmoid one. Tamplin & Gofman [illegible] is the only one that fits the beagle-dog data [illegible] a difference between the alpha and beta or [illegible]nalysis suggests, the direction is consistent [illegible] tissue recovery from effects of the two kinds [illegible]ations may be just as valid.

[illegible]es differ with the model is seen in the analysis [illegible] 1000 rads the projected risk (in man) in 50 [illegible]n-rads for a "low-dose linear model" and [illegible] a dose squared model. Thus the difference

[illegible]ted. Rosenblatt (146, 147) utilizes a three-[illegible] to account for simultaneous contributions [illegible] incidence in beagles receiving radium or [illegible] Cutler-Ederer life table method (148) for [illegible] the one at issue. This logistic type response [illegible] its age-related incidences to be calculated [illegible] incidence would occur at age 50 in the [illegible]long with risk evaluations based on it, by

[illegible] of bone tumor in mouse and dog receiving [illegible] square of the number of beta particles [illegible] body weight. This did not appear to hold, [illegible] generalizes that the data from mouse, [illegible]sentially equal radiosensitivity of the critical [illegible] phenomenon.

[illegible] et al (37) the linear nonthreshold model [illegible]dividuals per person-rad regardless of [illegible] the exposed group. This has not, in [illegible]effects of radiation although it is generally [illegible]. It almost never appears in chemical

[illegible] that none of the studies, man or animal,

[illegible] in shape of the curves fitting one model over the other are frequently less than the scatter of the data. Also, as Casarett (113) has recently pointed out, plotting together [illegible] of relations from different studies can give a spurious, usually spuriously linear, result. He also calls attention to the important fact that a sigmoid relationship seen in a relatively homogeneous animal population (homogeneous in terms not only of genetics but of exposure to contributing factors, environment, care, etc.) may reflect primarily the relative identity of thresholds in that population; thresholds might vary much more in a highly heterogeneous human population and the relation be less sigmoid and more linear.

Another facet of the intensive study of dose-response relations for radionuclides is the recent use of the "doubling-dose" concept. This was developed to handle data describing the genetic effects of radiation and is specifically the dose required to double the incidence rate of a given mutation. (NOTE: Some other genetic effects may rise as the square of the dose or by other functions). The concept is very dependent upon the particular kinetics of the genetic response, e.g., linear, cumulative, etc. Some authors (143, 151) have applied this concept to carcinogenesis induced by radionuclides as well as by external radiation. Fundamental to the argument is whether or not increase in incidence is in proportion to normal incidence rates or on an absolute basis. While the data brought [illegible] are primarily for external radiation, an ICRP analysis (152) does not in general support the former view. This makes considerable difference to the prediction of risk from the totality of various forms of cancer induced by radionuclides.

Blair ([illegible]) has used the dose response relation for radionuclides as a tool for inferring general mechanisms. [illegible] most recent studies (153, 154), the last [illegible] in beagles, skin tumor incidence in rats using the experiments of [illegible], Newman & Altschuler (15[illegible]), and lung cancer in uranium miners. In each case he concludes that there are [illegible] exclusive [illegible] by radiation. One, characteristic of high doses, is direct [illegible] of [illegible]genesis, the other, characteristic of low doses, requires a much lower initiating dose and follows only after a long latent period. He uses average skeletal dose from the several bone-seeking nuclides in the dogs, applied beta-radiation dose in the rats, and the inferred lung dose by calculation back from measured ^{210}Pb content of bone in the uranium miners (156, 157). He also assumes constant dose-rate, which is certainly not true but is an essential and not overly damaging simplification of the data. The initiating doses are [illegible] for the different nuclides but the latent period in the low dose domain [illegible]re or less constant for a given tumor type.

Müller [illegible] has considered Blair's concept and re[illegible] explanation [illegible] it is not significant [illegible] dose is given to one recipient or divided among [illegible] produce one case independently of the number of [illegible] that have collectively accumulated the dose.

Agreement to the data is as good as for Blair's original assumptions.

It is unfortunate that there is no independent evidence from biology [illegible] [illegible] [illegible] in oncogenesis and it is difficult to visualize how these could operate to produce a single low- and a single high-dose mechanism. Without such direct evidence the test of the theory rests heavily on fitting lines to data with considerable scatter.

The most needed information in the realm of dose-response relationships is as full and complete coverage as possible at low doses, an almost unending task; full ranges in single experiments, an expensive and time-consuming task; and information from cellular and tissue biology which would verify the models now being, if anything, overworked.

ENVIRONMENTAL ASPECTS

Fall-out from weapons testing.—The enormous activity generated by the "fall-out controversy" has greatly enhanced our knowledge of the metabolism and effects of the radionuclides produced in fission. In the period of this review the environmental surveillance activities begun by the AEC and later the U.S. Public Health Service have continued regularly. They show continued decrease in the amounts of radionuclides in the atmosphere and the biosphere which had their origin in fallout. The regular reports from the AEC's Health and Safety Laboratory in New York City and the several stations of the PHS network reported in "Radiological Health Data and Reports" should be consulted for details. The effects of Siberian, Chinese, and French tests on the inventory of fission products can readily be detected.

Typical and moderately recent reports on the amounts of fission products and related elements in the environment (158–171) show the behavior of the important nuclides to be predictable in broad terms but idiosyncratic in details. Remote corners of the world and their indigenous populations have been searched out and measured and some evidence gathered of especially high concentrations in simple plants and animal life in the arctic.

The passage of fall-out nuclides through food chains and their circulation in the troposphere and stratosphere can now be viewed as reasonably established despite the need for fuller understanding of many details (172–180). The 1970 IAEA symposium (180) is an especially useful compendium.

Direct measures of long-term effects of an acute fall-out exposure on man are, fortunately, represented by only one incident, the residents of the Marshall Islands in the Pacific, particularly Rongelap, and the crew of a Japanese fishing vessel involved in the same incident. The Rongelap group, which was exposed to fresh fall-out from the test of a thermonuclear device in 1954, has been diligently studied by a multi-disciplinary, multi-institutional group. The most notable internal contamination was with isotopes of iodine. Conard et al (181) report multiple nodules of the thyroid gland 10–14 years after the exposure in some of

... Blair's original assumptions.

...rmation points to a multiplicity of factors ... realize how these could operate to produce ...mechanism. Without such direct verification ...ting lines to data with considerable

...the realm of dose-response relationships is ...ble at low doses, an almost unending task; ...expensive and time-consuming task; and ...biology which would verify the models

...ENTAL ASPECTS

...enormous activity generated by the ...enhanced our knowledge of the metabolism ...duced in fission. In the period of this review ...begun by the AEC and later the U.S. ...regularly. They show continued decrease ...the atmosphere and the biosphere which had ...reports from the AEC's Health and Safety ...the several stations of the PHS network ...Data and Reports" should be consulted for ...and French tests on the inventory of ...

...reports on the amounts of fission products ... (158–171) show the behavior of the ...in broad terms but idiosyncratic in details. ...populations have been searched ...gathered of especially high concentrations ...the arctic.

...through food chains and their circulation in ...be viewed as reasonably established ...of many details (172–180). The 1970 ...useful compendium.

...of an acute fall-out exposure on man are, ...accident, the residents of the Marshall ...Rongelap, and the crew of a Japanese fishing ... The Rongelap group, which was exposed ...nuclear device in 1954, has been diligently ...national group. The most ... of iodine. Conard et al (181) ... years after the exposure ...

the Rongelap residents. The total cases are now 20 out of 64 exposees, 17 children ... adults. Calculated radiation doses to ...

Thyroid surgery on 11 children and ... matous nodules except for a "mixed papillary and follicular carcinoma" in one adult female. The lesions resemble those associated with iodine deficiency but the Marshallese natives eat large amounts of seafood and do not normally show iodine deficiency.

Growth and development retardation were also described in slight to moderate degree in some of the exposed children. Two male children developed atrophy of the thyroid and considerable growth retardation. The condition was considerably alleviated by treatment with thyroid hormone.

Exposees on neighboring islands that received considerably lower doses (by a factor of at least 2) have not shown any of the above changes with the exception of one nodular thyroid in an individual receiving about 40% of the dose calculated for the Rongelap residents. It cannot be stated with surety that this is radiogenic.

No leukemia has been seen in the exposed group. Fertility has been unchanged but the number of miscarriages and still-births was about a factor of 2 higher in the exposed women during the first 4 years after exposure. This has not continued since the initial period.

Of special importance is the delay in development of these effects of iodine in fall-out. Until the mid-1960s, i.e., for over 10 years after exposure, the exposed people gave no obvious evidence of thyroid abnormality.

Other populations have received more than the world-wide dose from fall-out but these have not and cannot be studied with the precision of the Marshallese group. For example, a group of children (4827 examined) in St. George, Utah received low but significant exposures to fall-out from some of the early Nevada tests. This population, exposed in the early 1950s, has proven difficult to study. Estimated doses in the most exposed group range from 84–120 rads Av (182, 183) obtained primarily by drinking contaminated milk. Attempts to find thyroid nodules or other pathology in this group correlatable with ingestion of contaminated milk have not been successful. Hoffman (184) concludes that "based on the available data with its limitations, the exposure received by the children does not appear to have caused any significant increase in thyroid neoplasia." Barring unexpected new findings, it must be concluded that this group will not yield any further information.

Beginning in the late 1960s, Sternglass has contended that there is a causal association between the deposition of fall-out nuclides, particularly ^{90}Sr, and infant and fetal mortality, including a greater than expected incidence of childhood leukemia. Since he is now applying the same views to radionuclide discharges from nuclear energy installations, the discussion will be postponed to the following section.

Discharge of radionuclides from nuclear energy installations.—The environmental impact of actual and potential discharge of radionuclides from nuclear power reactors, fuel reprocessing facilities, and nuclear research and development laboratories is an active, indeed crucial, issue at the present time. Decisions made now regarding the biological impact of such released nuclides and the probability of their occurrence may well determine the direction of our future technology. Some of the major issues will be examined here. Many summaries are available (180, 185).

The biological problems devolve again upon the true shape of the dose-response relationship, although for practical purposes the conservative assumption is made that the linear no-threshold model holds. Also, all installations must show that they are maintaining the *lowest practicable* release levels, regardless of general standards (140).

The primary considerations are (*a*) evidence of effects from past activities, (*b*) actual and potential release rates and their impact, and (*c*) the role of the ecosystem.

Evidence of effects from past activities.—Except for the rare instances of accidental releases of significant quantities of radionuclides, all inferences regarding effects of past activities involve the epidemiological approach. Sternglass (186–189) correlates increases in fetal death rate (actually a lesser declining slope on a long-continuing decrease in rate which he terms an "excess mortality") with infant mortality in Albany-Troy, N.Y., New York State vs California, Missouri, the entire United States compared to Sweden, and the like with the time of arrival of fall-out from the Nevada tests, USSR tests, and Pacific thermonuclear tests. For nuclear facilities he relates excess infant mortality to routine radionuclide emissions from boiling water reactors in Illinois, Michigan, California, Pennsylvania, and New York, a fuel reprocessing facility in western New York, the Hanford Atomic Products Works at Richland, Washington and to Brookhaven National Laboratory on Long Island (190–192). Even the small educational and testing reactors are linked, by Sternglass, to deleterious effects on children living in the neighborhood. In all cases the effect is described as "excess mortality" within a rather circumscribed geographical area "downwind" of the facility after a variable latent period, and due to radionuclides released in its operation. These claims, many of them made in public hearings and proceedings, have generated considerable concern in the general public and government alike.

Sternglass does not estimate doses to the recipients but any reasonable calculation from the levels of release, or even multiples thereof, indicates the radiation dose to be very small. Thus, very great radiosensitivity of the embryo and fetus is implied by his conclusions. While diligent laboratory studies of the relative sensitivity of the fetus and newborn in animals (12) clearly show greater sensitivity than adults or even the young beyond infancy, the factors of difference do not approach those necessary to account for the mortality rates attributed to radionuclide exposures. Thus, the human embryo and fetus must be considerably more sensitive than any of the animal populations studied, to substantiate the proposition made by Sternglass.

[illegible]lities, and nuclear research and develop- [illegible] crucial, is [illegible] at the present time. Decisions [illegible] impact of such released nuclides and the [illegible] well determine the direction of our future [illegible] will be examined here. Many summaries

[illegible] again upon the true shape of the dose- [illegible] practical purposes the conservative assump- [illegible]eshold model holds. Also, all installations [illegible] the *lowest practicable* release levels, regard-

[illegible] evidence of effects from past activities, [illegible] and their impact, and (*c*) the role of the

[illegible]*ctivities.*—Except for the rare instances of [illegible] quantities of radionuclides, all inferences [illegible] involve the epidemiological approach. Stern- [illegible] in fetal death rate (actually a lesser declining [illegible] in rate which he terms an "excess mortality") [illegible] Troy, N.Y., New York State vs California, [illegible] compared to Sweden, and the like with the [illegible] Nevada tests, USSR tests, and Pacific thermo- [illegible] he relates excess infant mortality to routine [illegible] water reactors in Illinois, Michigan, [illegible] York, a fuel reprocessing facility in western [illegible] Products Works at Richland, Washington and [illegible] on Long Island (190–192). Even the small [illegible] are linked, by Sternglass, to deleterious effects [illegible]hood. In all cases the effect is described as [illegible] circumscribed geographical area "down- [illegible] latent period, and due to radionuclides [illegible] claims, many of them made in public hearings [illegible] considerable concern in the general public

[illegible] to the recipients but any reasonable cal- [illegible] or even multiples thereof, indicates the radia- [illegible] very great radiosensitivity of the embryo and [illegible] diligent laboratory studies of the relative [illegible] animals (12) clearly show greater sensitivity [illegible] infancy, the factors of difference do not [illegible] for the mortality rates attributed to radio- [illegible] embryo and fetus must be considerably [illegible] populations studied, to substantiate the

There have been many and voluminous refutations of these claims (193–202) and it is impossible to detail them here. The primary criticisms relate first to the lack of an epidemiologically suitable population in either size or composition, lack of consideration of changes in socio-economic status of the various populations, lack of convincing evidence that other environmental and endemic factors have been excluded or accounted for, and lack of statistical rigor in handling the data. This criticism has come largely from epidemiologists and statisticians. Secondly, others take issue with the figures used for fall-out distribution, wind directions, and other aspects of the exposure situation, and state that the situation was not as described. Finally some of the criticisms imply selection of the data. While these criticisms do not show conclusively that there is no such effect, they place the burden of proof on the protagonist.

There have been a few other similar claims but involving cancer incidence in the entire population, e.g., Weik (203) cites increased cancer incidence in a small population living near the Indian Point, New York nuclear station. The statistical and epidemiological suitability of such a small population is in doubt. Fadeley (204) presents data showing increased malignancy incidence for populations in certain counties in Oregon living near, or influenced by, the Columbia River. He attributes this to the radionuclides discharged from the Hanford Atomic Products operation upstream at Richland, Washington. The data were deemed not to support the conclusions by Bailar & Young (205) because several pertinent [illegible] counties were omitted without explanation, basic data on actual numbers of deaths were not supplied, there was a lack of age or sex adjustment for counties known to vary in these parameters, and there was no accounting for the difference in cancer mortality known to occur between urban and rural populations, and the urban populations are more likely to be along the river than elsewhere.

Actual or potential release rates.—[illegible] or potential release rates of radionuclides from nuclear energy installations have been documented for many years—better than those for most other environmental pollutants. Currently the documentation of the chemical [illegible] releases is catching up. Using these figures, effects can be argued from studies in animals and man at higher doses. The releases, while usually small on the basis of concentration per unit volume, sometimes amount to thousands of curies on an integral basis and the gradual build-up in the environment is a source of concern. On the other hand, except in a major incident, these releases contribute only a small fraction above natural background to the general level of radiation in the environment.

On the linear no-threshold theory some detrimental effect is assumed to occur at any radiation dose and [illegible] in the recent literature is based upon [illegible] the [illegible] judged to balance or outweigh the risks. This is [illegible] to do on a scientific and technical basis alone, nor should it be [illegible].

The role of the ecosystem.—The potential for toxic effects in man of radionuclides released to the environment depends greatly upon the processes involved in transferring the nuclides from release point or mode to intake by man. Much of the burgeoning field of radioecology is devoted to studies on this aspect. Some nuclides such as plutonium in its most common form, are so insoluble that they are unlikely to move from the environment to man in significant quantity except by direct inhalation or a contaminated wound (206, 207). Other nuclides may tend to concentrate in one or more organism or vector in the ecosystem. Ultimate accumulation in man depends upon whether or not this critical step is involved or by-passed. Concentration factors of several thousand are not uncommon (208).

Much effort has been and is being expended in identifying critical pathways (209, 210) e.g., air-leaf-cow-milk-body versus air-soil-plant-cow-milk-body. Recent work makes it clear that foliar absorption of many nuclides is sufficiently greater than that through root systems to make the first the "critical pathway" e.g. ^{90}Sr in many instances. However, this is not the critical pathway if milk or dairy products are not consumed. In this event, the critical pathway may instead be through grain as is the case in the Orient, and the resultant intake may be quite different.

Another aspect is the identification of critical nuclides (209, 211). The isotopic composition of discharges differs with the type of reactor and the time of operation, and it is different for a fuel processing facility than for a reactor. Thus, the critical pathway will not necessarily be the same for different types of operation. Of special concern has been the possibility of an undetected critical pathway or critical nuclide. The role of zinc-65, for example, was not appreciated until Japanese investigators drew attention to it (212). The primary likelihood for such a finding now is in aquatic environments, especially oceanic (213, 214), and in the development of different fuel cycles.

Not to be forgotten either, is the role of time, since isotopes of importance in fresh fission products become less significant later on. Indeed, if times are long as in the consideration of radioactive waste disposal, some very unexpected nuclides become "critical" to the evaluation of potential hazard (18).

An excellent summary of the factors to be considered in the instance of a single river system in Europe is seen in the paper by Feldt (215).

Radionuclide effects on "lower" organisms.—Quite apart from the movement of radionuclides through an ecosystem to man is the possibility of deleterious effects in lower organisms. This assumes importance to man in proportion to the importance of that organism to the ecosystem or as a member of a food chain. Radiation effects have now been clearly demonstrated in highly contaminated systems under control, such as White Oak Lake at Oak Ridge. Hundreds of studies have been directed at determining the radiosensitivity of animals, plants, microorganisms, and even full ecosystems such as a tropical rainforest. While there have been some surprises, e.g., the relatively high sensitivity of conifers compared to deciduous trees, and marked differences in sensitivity at different stages of development in most organisms, no key organism has yet appeared with such exquisite sensitivity and in a key position in an ecosystem to negate

...lease point of mode to intake by man. Much
...gy is devoted to studies on this aspect. Some
...st common form, are so insoluble that they
...onment to man in significant quantity except
...nated wound (206, 207). Other nuclides may
... organism or vector in the ecosystem. Ultimate
... whether or not this critical step is involved
... of several thousand are not uncommon

...ing expended in identifying critical pathways
...-body versus air-soil-plant-cow-milk-body.
...air absorption of many nuclides is sufficiently
...ems to make the first the "critical pathway"
...ver, this is not the critical pathway if milk or
... in this event, the critical pathway may instead
... the Orient, and the resultant intake may be

...tion of critical nuclides (209, 211). The isotopic
... with the type of reactor and the time of opera-
...rocessing facility than for a reactor. Thus, the
...ay be the same for different types of operation.
...ossibility of an undetected critical pathway or
..., for example, was not appreciated until
...ation to it (212). The primary likelihood for
... environments, especially oceanic (213, 214),
...nt fuel cycles.
...e role of time, since isotopes of importance in
...significant later on. Indeed, if times are long,
...ctive waste disposal, some very unexpected
... evaluation of potential hazard (18).
...actors to be considered in the instance of a
...en in the paper by Feldt (215).

...organisms.—Quite apart from the movement
...stem to man is the possibility of deleterious
...comes importance to man in proportion to the
... ecosystem or as a member of a food chain.
...clearly demonstrated in highly contaminated
... Oak Lake at Oak Ridge. Hundreds of
...ing the radiosensitivity of animals, plants,
...tems such as a tropical rainforest. While
...the relatively high sensitivity of conifers
...ed differences in sensitivity at different
..., no key organism has yet appeared
... a key position in an ecosystem to negate

entirely the general concepts derived from studies with higher vertebrates (2..).

There are some findings that clearly need further explanation. For example, Polikarpov (217) reports from extensive studies with marine and freshwater fish eggs that hatching of larvae is reduced even at 10^{-5} pCi/l of certain isotopes. Also, the oceanic environment is so vast that we cannot feel fully confident we have any more than begun the study of its radioecology (213). It is hoped a subsequent review can devote special attention to some of these problems.

SPECIAL PROBLEMS

Tritium and transmutation.—Entering the body as tritiated water, tritium (^3H) distributes as body water and any radiation effects produced are comparable to whole body irradiation. When it enters in organic form, particularly as a label for nucleic acid precursors, it may be incorporated into vital structures such as DNA. This latter has led to much concern that its effects, especially genetic and carcinogenic, might be much greater than the calculated radiation dose would predict. That such concern was largely unfounded was shown by Bond & Feinendegen (218) in 1966. But the concern has continued in both scientific and lay circles and has become part of the "nuclear power controversy."

A full re-examination of all aspects of the problem was presented by Bond (219). His conclusion is that in higher organisms, at least, all effects of tritium can be accounted by the radiation dose delivered and have the same radiobiological meaning as a similar dose from X or alpha rays of the same dose pattern. Also just recently the ICRP (220) and NCRP (140) have revised an earlier recommendation that a quality factor of 1.7 be applied in calculating rem doses for tritium and other very low energy electrons or photons. The factor has been returned to 1.0.

One of the flaws in the earlier reasoning seems to have been the misunderstanding that the range of the beta particle even from a low-energy source such as tritium is actually long compared to the cross-section or other reasonable measure of DNA as a target. No special local deposition of energy should be expected except for Bragg-Gray considerations.

A residual concern is the so-called transmutation effect (change of parent atom to one of different atomic number, usually plus local recoil and excitation energy). Re-examination of this possible effect not only for ^3H but for other incorporated isotopes, e.g., ^{32}P, shows (218, 221) that a transmutation effect does exist sometimes in eukaryotic cells but not in prokaryotic cells except under special circumstances. These special circumstances involve specific molecular arrangements such as cytosine tritiated in the five position and incorporated into DNA of growing cells (222). Since considerable effort must be expended to produce such labelling and incorporation it can be concluded that transmutation effects play a minor role, if any, in prokaryotic cells.

Cahill & Yuile (223) have recently described effects of continuous exposure to tritiated water on pregnant rats. The calculated radiation dose was from 0.3–30.0 rads/day. The higher doses produced microencephaly, sterility, stunting, reduction of litter size and weight. The stunting persisted in the males from mothers carrying above [illegible] μCi/ml but not in the females. They concluded [illegible] continuous presence of HTO activity at a level of [illegible] μCi/ml is compatible with normal reproduction in the rat. This argues further against any special toxicity of tritium in the gravid mammal. However the experiments were not extended to further generations or a search for genetic changes.

No isotope effect such as that seen with deuterium has been described for tritium. Many other aspects of tritium toxicology can be found in the review by Jacobs (224) and recent symposia (e.g. 225).

ACKNOWLEDGEMENTS

Many thanks go to the numerous colleagues who sent me their reprints and bibliographies; regrets to many whose work could not be quoted because of space limitations and the necessity to omit certain whole areas. Special thanks are proffered to those who responded so thoughtfully and helpfully to the mini-questionnaire requesting their views on recent advances. Secretarial help "beyond the call of duty" was supplied by Miss Rose Sternberg and Mrs. D. C. O'Neil.

LITERATURE CITED[3]

1. Nelson, N. 1969. In *Biological Implications of the Nuclear Age*, 223–30, Proc. Symp. Lawrence Rad. Lab.
2. Catsch, A. 1963. *Ann. Rev. Pharmacol.* 3:243–66
3. [illegible] F. W. 1963. *Radioisotopes in the Human Body: Physical and Biological Aspects*. New York: Academic 346 pp.
4. Mays, C. W. [illegible] eds. 1969. *Delayed Effects of Bone-Seeking Radionuclides*, Salt Lake City: Univ. Utah Press 513 pp.
5. Hanna, M. G., Jr., Nettesheim, P., Gilbert, J. R. eds., 1970. *Inhalation Carcinogenesis*. AEC Symp. Ser. 13, Springfield, Va.: USAEC [illegible] pp.
6. Moskalev, Y. I. ed. 1966. (Moscow) *Distribution and Biological Effects of Radioactive Isotopes*. Washington: USAEC 1968 AEC-tr-6944 (Rev) transl. 713 pp.
7. Moskalev, Y. I. ed. 1969 (Moscow) *Radioactive Isotopes and the Body*. Springfield, Va.: USAEC 1971 AEC-tr-7195 Transl. 439 pp.
8. Stannard, J. N., Casarett, G. W. Eds. 1964. *Radiat. Res. Suppl.* 5:[illegible]–437

[3] U.S.A.E.C. reports can be viewed at any of the depository libraries listed in *Nuclear Science Abstracts* or purchased as photocopy from Microsurance, Inc., Oak Ridge Microreproduction Center, P.O. Box 3522, Oak Ridge, Tennessee 37830. Other "in-house" U.S. Government [illegible] documents and recent AEC documents are available from the National Technical Information Service, U.S. Department of Commerce, Springfield, Virginia 22151, and Congressional Hearings, etc., from the U.S. Government Printing Office (Superintendent of Documents). The International Atomic Energy Agency (IAEA) documents [illegible] Inc., P.O. Box 433, New York, N.Y. [illegible] International Commission on Radiological Protection (ICRP) [illegible] Pergamon Press for most of [illegible] the National Council on Radiation Protection and Measurement reports can be ordered through NCRP Publications, P.O. Box [illegible], Washington, D.C. 20008. Also, the author will be glad to assist readers having difficulty locating any of the quoted reference material.

The stunting persisted in the males from [illegible] but not in the females. They conclude that [illegible] at a level of 1.0 uCi/ml is compatible [illegible]. This argues further against any special [illegible]. However the experiments were not [illegible] search for genetic changes.

[illegible] with deuterium has been described for [illegible] toxicology can be found in the review [illegible] (e.g. 225).

[illegible]WLEDGEMENTS

[illegible] colleagues who sent me their reprints and [illegible] work could not be quoted because of [illegible] to omit certain whole areas. Special thanks [illegible] so thoughtfully and helpfully to the mini-[illegible] recent advances. Secretarial help "beyond [illegible] Miss Rose Sternberg and Mrs. D. C. O'Neil.

[illegible]ERATURE CITED[3]

[illegible] Gilbert, J. R. eds., 1970. *Inhalation Carcinogenesis.* AEC Symp. Ser. 18, Springfield, Va.: USAEC 515 pp.

6. Moskalev, Y. I. ed. 1966. (Moscow) *Distribution and Biological Effects of Radioactive Isotopes.* Washington: USAEC 1968 AEC-tr-6944 (Rev) Transl. 713 pp.
7. Moskalev, Y. I. ed. 1969 (Moscow) *Radioactive Isotopes and the Body.* Springfield, Va.: USAEC 1971 AEC-tr-7195 Transl. 439 pp.
8. Stannard, J. N., Casarett, G. W. Eds. 1964. *Radiat. Res.* Suppl. 5:1–437
9. WHO-IAEA. 1963. *Diagnosis and Treatment of Radioactive Poisoning.* Vienna: IAEA (STI/PUB/65) 449 pp.
10. Kornberg, H. A., Norwood, W. D. eds. 1968. *Diagnosis and Treatment of Deposited Radionuclides.* Monograph on Nucl. Med. & Biol. No. 2, Excerpta Medica Found. The Netherlands 671 pp.
11. Cloutier, R. J., Edwards, C. L., Snyder, W. S., Eds. 1970. *Medical Radionuclides: Radiation Dose and Effects.* AEC Symp. Ser. 20. Springfield, Va.: USAEC 515 pp.
12. Sikov, M. R., Mahlum, D. D. eds. 1971. *Radiation Biology of the Fetal and Juvenile Mammal.* AEC Symp. Ser. 17. Washington: USAEC 1021 pp.
13. Commission of the European Communities. 1971 *Radiation Protection Problems Relating to Transuranium Elements (Seminar).* Luxembourg: CID 669 pp.
14. Stover, B. J., Jee, W. S. S. eds. 1972. *Radiobiology of Plutonium.* Salt Lake City: Univ. Utah Press, 539 pp.
15. Goldman, M., Bustad, L. K., eds. 1971 *Biomedical Implications of Radiostrontium Exposure.* AEC Symp. Ser. 25: Springfield, Va.: USAEC 396 pp.
16. Thompson, R. C., Bair, W. J. eds. 1972. The Biological Implications of the Transuranium Elements. — Proc. Symp. Richland, Wash. *Health Phys.* 22: [illegible]33–943
17. IAEA-WHO 1969 *Radiation Induced Cancer.* Vienna: IAEA STI-PUB 228, 495 pp.
18. Hodge, H. C., Hursh, J. B., Stannard, J. N. eds. 1973. Handbook Exp. Pharm. Vol. 36 *Uranium, Plutonium and the Transplutonic Elements.* Hamburg: Springer-Verlag, In press
19. Bair, W. J. See Ref. 5, 77–94
20. Saenger, E. L. ed. 1963. *Medical Aspects of Radiation Accidents* Washington: USAEC 274 pp.
21. Stover, B. J. 1972. *Health Phys.* 2[illegible]
22. Moroz, B. B., Parfenov, Yu, D. 1972. *Atomic [illegible] Rev.* (IAEA) 10: [illegible]
23. [illegible] Kuznetsyandskaya, L. B. [illegible] vols. on *The [illegible] Radioactive Substances* [illegible]
24. [illegible] 1964. [illegible] Sr, Ru, Ce, Ra
25. [illegible] 1970. [illegible] Radioactive Co, Na, P, Au
26. Ibid 1967. vol. 3 Iron
27. Ibid 1970. vol. 4 ^{232}Th, ^{235}U
28. Ibid 1970. vol. 5 ^{65}Zn
29. Ovakimov, V. G. 1970. See Ref. 28, 40–45
30. Ovakimov, V. G., Bibikhin, L. M., 1970, See Ref. 28, 46–59
31. Orlynskaya, R. L. 1970. See Ref. 28, 96–105
32. Filatov, P. P. 1970. See Ref. 28, 124–37
33. Finkel, M. P., Biskis, B. O., 1969. See Ref. 4, 417–35
34. Brues, A. M., Grube, D. D., Auerbach, H. 1970. *Ann. Rep. Bio. Med. Div.*, Argonne Nat. Lab., ANL-7770, 48–51
35. Calvin, M. 1972. *Radiat. Res.* 50: 105–19
36. Stover, B. J., Eyring, H. 1970. *Proc. Nat. Acad. Sci.* 66:132–39
37. Evans, R. D., Keane, A. T., Shanahan, M. M. 1972. See Ref. 14, 431–67
38. Blair, H. A. 1964. See Ref. 8, 216–27
39. Stannard, J. N., Blair, H. A., Baxter, R. C. 1964. See Ref. 8, 229–45
40. Finkel, A. J., Miller, C. E., Hasterlik, R. J. 1969. See Ref. 4, 195–225
41. Rowland, R. E., Failla, P. M., Keane, A. T., Stehney, A. F. 1970. *Ann. Rep. Radiol. Phys. Div. Argonne Nat. Lab.* ANL-7760, 1–17
42. Ibid 1971. ANL-7860, Pt II
43. Spiess, H. 1969. See Ref. 4, 227–47
44. Spiess, H., Mays, C. W. 1972. *Hanford Radionuclide Carcinogenesis Symp.* Richland, Wash. In Press
45. Spiess, H., Mays, C. W. 1970. *Health Phys.* 19:713–29
46. Casarett, A. P. 1968. *Radiation Biology.* Englewood Cliffs: Prentice-Hall. 368 pp. (esp. pp. 111–12, 129–32)
47. Lorenz, E. 1944. *J. Nat. Cancer Inst.* 5:1–15
48. Joint Comm. on Atomic Energy, 1967. 90th Congress of the U.S. *Hearings on Radiation Exposure of Uranium Miners.* Pts. 1 & 2 Washington: U.S. Govt. Printing Off.
49. Ibid. 91st Congress. 1969. *Hearings on Radiation Standards for Uranium Mining.* Washington: U.S. Printing Off.
50. Lundin, F. E., Jr., Wagoner, J. K., Archer, V. E. 1971. *Radon Daughter Exposure and Respiratory Cancer, Quantitative and Temporal Aspects.* Rep. from Epidemiol. Study of U.S. Uranium Miners, NIOSH-NIEHS Joint Monograph No. 1, Springfield, Va.: 176 pp.

[illegible] at any of the depository libraries listed in *Nuclear* [illegible] Photocopy from Microsurance, Inc., Oak Ridge [illegible] 3522, Oak Ridge, Tennessee 37830. Other "in-[illegible] and recent AEC documents are available from the [illegible] U.S. Department of Commerce, Springfield, [illegible], etc., from the U.S. Government Printing [illegible] The International Atomic Energy Agency [illegible] Inc. P.O. Box 433, New York, N.Y. [illegible] Radiological Protection (ICRP) uses Pergamon [illegible] on Radiation Protection and Measure-[illegible] Publications, P.O. Box 4867, Washington [illegible] to assist readers having difficulty locating any

51. Stannard, J. N., Casarett, G. W. 1964. See Ref. 8. 5:398–54
52. *Radiation Exposure of Uranium Miners*. 1968. Rep. Advisory Committee, Div. Med. Sci.; Nat. Acad. Sci., Nat. Res. Council, Nat. Acad. Eng. 31 pp.
53. Morken, D. A. 1969. *Health Phys.* 16:796–98
54. Pasternack, B. S. 1971. In *Research in Environmental Health Sciences*. Eighth Ann. Rep. Es00260, N.Y.U. Med. Ctr., 185
55. Federal Radiation Council, 1967. Rep. No. 8. Revised. *Guidance for the Control of Radiation Hazards in Uranium Mining*. 60 pp.
56. Interagency Uranium Mining Radiation Review Group. Rep. Subgroup I.B. 1971. *Summary and Conclusions*. 5 pp.
57. National Academy of Sciences, National Research Council. 1971. Rep. Ad Hoc Comm. Advisory Comm. Fed. Radiat. Counc. *Epidemiologic Studies of Uranium Miners*. 6 pp.
58. Saccomanno, G., Archer, V. E., Auerbach, O., et al. 1971. *Cancer* 27:515–23
59. Kotin, P. 1970. Rep. Chairman Subgroup IV-A Interagency Uranium Mining Radiation Review Group. *Diagnosis and Therapy of Lung Cancer*. 5 append. 30 pp.
60. Yuile, C. L., Berke, H. L., Hull, T. 1967. *Radiat. Res.* 31:760–74
61. Stuart, O., Busch, R. H., Palmer, R. F. 1972. *Studies of the Effects of Inhaled Radon Daughters, Uranium Ore Dust, and Diesel Exhaust in Hamsters*. Presented at 17th Ann. Meet. Health Phys. Soc. Las Vegas, Nev., P/67, Abstr. p. 19
62. Stuart, B. O. et al. 1971. In Ann. Rep. 1970, Pacific Northwest Labs., BNWL-1550, Pt 1, 86–90
63. Stuart, B. O., Willard, D. H., Howard, E. B. 1970. See Ref. 5, 413–27
64. Kilibarda, M., Višnjić, V., Panov, D., Radovanović, R., Novak, L. 1968. See Ref. 10, 222–33
65. Swarm, R. L., ed. 1967. *Distribution, Retention, and Late Effects of Thorium Dioxide*. Ann. NY Acad. Sci. 145:523–858
66. IAEA-WHO 1968. *The Dosimetry and Toxicity of Thorotrast*. Tech. Rep. IAEA-106. IAEA Vienna 173 pp.
67. Faber, M. Ibid, pp. 139–46
68. Faber, M. 1967. See Ref. 65, 8[illegible]
69. da Silva Horta, J., Abbatt, J. D., Cayolla da Motta, L., Roriz, R. 1965. See Ref. 66, 147–51
70. Tsukamoto, K. 1968. Ibid, 152–56
71. Abbatt, J. D. 1968. Ibid, 157–59
72. Abbatt, J. D. 1967. See Ref. 65, 767–75
73. Muth, H., et al. 1971. 4th U.N. Int. Conf. Peaceful Uses Atomic Energy, Geneva, Switzerland. AED-CONF-71-100-51, 18 pp.
74. Norwood, W. D. 1972. See Ref. 14, 531–37
75. Langham, W. H. 1972. *Health Phys.* 22:943–62
76. Durbin, P. 1972. See Ref. 14, 469–30
77. Dougherty, T. F., Mays, C. W. 1969. IAEA-SM-118/3, pp. 361–67
78. Mays, C. W., Dougherty, T. F. 1972. *Health Phys.* 22:793–801
79. Mays, C. W., Lloyd, R. D. 1972. See Ref. 14, 409–30
80. Finkel, M. P., Biskis, B. O. 1968. *Progr. Exp. Tumor. Res.* 10:72–111
81. Buldakov, L. A., Lyubchanskii, E. R., Moskalev, Y. I., Nifatov, A. T. 1969. (Moscow) *Problems of Plutonium Toxicology*. Springfield, Va.: USAEC 1970 (LF-tr-41) Transl. A. A. Horvath. 210 pp.
82. Langham, W. L., Healy, J. 1973. Chap. 12, Ref. 18. In press
83. Vaughn, J., Bleaney, B., Taylor, D. M. 1973. Chap. 10, Ref. 18, In press.
84. Mays, C. W., Taylor, G. N., Jee, W. S. S., Dougherty, T. F. 1970. *Health Phys.* 19:601–10
85. Buldakov, L. A., Lyubchanskii, E. R. 1970. *Argonne Nat. Lab. Transl. ANL-TRANS-864*. Manuscript furnished by Y. I. Moskalev to A. Lindenbaum. (Nov. 1970)
86. Finkel, M. P., Biskis, B. O. 1962. *Health Phys.* 85:65–79
87. Lloyd, E., Marshall, J. H. 1972. See Ref. 14, pp. 377–83
88. Park, J. F., Bair, W. J., Busch, R. H. 1972. *Health Phys.* 22:803–10
89. Bair, W. J., Ballou, J. E., Park, J. F., Sanders, C. L. 1973. Chap. 11. See Ref. 18. In press
90. Yuile, C. L., Gibb, F. R., Morrow, P. E. 1970. *Radiat. Res.* 44:821–33
91. Howard, E. B. 1970. *[illegible] of Experimental Respiratory [illegible]gen*, 147–60. AEC Symp. Ser. No. 21, Springfield, Va., USAEC
92. Lebel, J. L., Bull, E. H., Johnson, L. J., Watters, R. L. 1970. *Am. J. Vet. Res.* 31:1513–16
93. McClanahan, B. J., Howard, E. B.

68. Faber, M. 1967. See Ref. 65, 843–48
69. da Silva Horta, J., Abbatt, J. D., Cayolla da Motta, L.A.C.R. 1968. See Ref. 66, 147–51
70. Tsukamoto, K. 1968. Ibid, 152–56
71. Abbatt, J. D. 1968. Ibid, 157–59
72. Abbatt, J. D. 1967. See Ref. 65, 767–75
73. Muth, H., et al. 1971. 4th U.N. Int. Conf. Peaceful Uses Atomic Energy, Geneva, Switzerland. AED-CONF-71-100-51, 18 pp.
74. Norwood, W. D. 1972. See Ref. 14, 531–37
75. Langham, W. H. 1972. *Health Phys.* 22:943–62
76. Durbin, P. 1972. See Ref. 14, 469–30
77. Dougherty, T. F., Mays, C. W. 1969. IAEA-SM-118/3, pp. 361–67
78. Mays, C. W., Dougherty, T. F. 1972. *Health Phys.* 22:793–801
79. Mays, C. W., Lloyd, R. D. 1972. See Ref. 14, 409–30.
80. Finkel, M. P., Biskis, B. O. 1968. *Progr. Exp. Tumor. Res.* 10:72–111
81. Buldakov, L. A., Lynbchanskii, E. R., Moskalev, Y. I., Nifatov, A. T. 1969. (Moscow) *Problems of Plutonium Toxicology.* Springfield, Va.: USAEC 1970 (LF-tr-41) Transl. A. A. Horvath. 210 pp.
82. Langham, W. L., Healy, J. 1973. Chap. 12, Ref. 18. In press
83. Vaughn, J., Bleaney, B., Taylor, D. M. 1973. Chap. 10, Ref. 18, In press.
84. Mays, C. W., Taylor, G. N., Jee, W. S. S., Dougherty, T. F. 1970. *Health Phys.* 19:601–10
85. Buldakov, L. A., Lyubchanskii, E. R. 1970. *Argonne Nat. Lab. Transl. ANL-TRANS-864.* Manuscript furnished by Y. I. Moskalev to A. Lindenbaum. (Nov. 1970)
86. Finkel, M. P., Biskis, B. O. 1962. *Health Phys.* 85:65–79
87. Lloyd, E., Marshall, J. H. 1972. See Ref. 14, pp. 377–83
88. Park, J. F., Bair, W. J., Busch, R. H. 1972. *Health Phys.* 22:803–10
89. Bair, W. J., Ballou, J. E., Park, J. F., Sanders, C. L. 1973. Chap. 11. See Ref. 18. In press
90. Yuile, C. L., Gibb, F. R., Morrow, P. E. 1970. *Radiat. Res.* 44:821–33
91. Howard, E. B. 1970. *Morphology of Experimental Respiratory Carcinogen.*, 147–60 AEC Symp. Ser. No. 21, Springfield, Va.: USAEC
92. Lebel, J. L., Bull, E. H., Johnson, L. J., Watters, R. L. 1970. *Am. J. Vet. Res.* 31:1513–16
93. McClanahan, B. J., Howard, E. B., Ragan, J. A., Beamer, J. L. 1968. *Pacific N.W. Lab. Ann. Rep. BNWL-714*, 1:1.32–1.34
94. Rosenthal, M. W., Lindenbaum, A. 1969. See Ref. 4, 371–86
95. Della Rosa, R. J., Stannard, J. N. 1969. See Ref. 5, 205–15
96. Ballou, J. E., Thompson, R. C., Clarke, W. J., Palotay, J. L. 1967. *Health Phys.* 13:1087–92
97. Taylor, D. M., Bensted, J. P. M. 1969. See Ref. 4, 357–70
98. Leach, L. J., et al 1971. Abstr. *Health Phys. Meet.*, Paper P.28, H.P. 21:15. Also Health Phys. In press
99. Morrow, P. E., Gibb, F. R., Beiter, H. 1972. *Health Phys.* 13:273–80
100. Hopkins, B. J. H. 1972. See Ref. 15, 326–33
101. Nelson, N. S., Berman, E., Rosenstein, L. S., Ward, J. M., Wright, J. F. 1972. See Ref. 15, 182–206
102. Volf, V. 1972. See Ref. 15, 313–25
103. Finkel, M. P., Biskis, B. O., Greco, I., Camden, R. W. 1972. See Ref. 15, 285–312
104. Dougherty, J. H., Taylor, G. N., Mays, C. W. 1972. See Ref. 15, 259–78
105. Dougherty, T., Mays, C. W. 1969. See Ref. 17, 361–67
106. Clarke, W. J. et al 1972. See Ref. 15, 242–58
107. Pool, R. R., Williams, R. J. R., Goldman, M. 1972. See Ref. 15, 277–84
108. McClellan, R. O., Jones, R. K. 1969. See Ref. 4, 293–322
109. McClellan, R. O. et al. 1972. See Ref. 15, 149–67
110. Mays, C. W., Lloyd, R. D. 1972. See Ref. 15, 352–57
111. Müller, J. 1970. "Effects of Chronic Irrad. and Eval. of Risk from Incorporated ^{90}Sr & ^{226}Ra in Man". *Monographia XLX*, Univ. Karlova, Praha, Acta Univ. Carolinae Medica. 5–135
112. Rowland, R. E. 1969. See Ref. 17, 3–[illegible]
113. Casarett, G. W. 1972. *Hanford Symp. Radionuclide Carcinogen.* In press
114. ICRP Publ. 8. 1966. *The Evaluation of Risks from Radiation.* Oxford: Pergamon. [illegible] pp.
115. [illegible] Thomas, G. E., [illegible] 1968. *J. [illegible] Med.* [illegible]
116. [illegible] 1970. See Ref. 11, [illegible]–40
117. [illegible], W., Jr., Colvin, M. 1965. *Int. J. Radiat. Biol.* 10:391–401
118. Moore, W., Jr., Colvin, M. 1968. *J. Nucl. Med.* 9:165–67
119. Castoldi, S. J., Schmickel, R. D., Bath, M., Cisar, C. F. 1966. *New Eng. J. Med.* 275:739–45
120. Thomas, R. L., Scott, J. K., Chiffelle, T. L. 1970. *AIHA J.* 31:213–20
121. Sanders, C., Thompson, R., Bair, W. J. 1970. See Ref. 5, 285–303
122. Thomas, R. L., Scott, J. K., Chiffelle, T. L. 1972. *Radiat. Res.* 49:589–610
123. Berke, H. L., Dettch, D. 1970. See Ref. 5, 429–32
124. Marinelli, L. D., Quimby, E. H., Hine, G. J. 1948. *Am. J. Roentgenol.* 59:260–80
125. Greenfield, M. A., Lane, R. G. 1971. *Nucl. Med.*, 2nd Ed., ed. W. H. Bland. 101–28. New York: McGraw-Hill
126. Loevinger, R. 1970. See Ref. 11, 481–84
127. Medical Internal Rad. Dose Comm. 1968. Pamphlets 1–3. Suppl. 1. *J. Nucl. Med.*
128. Ibid, Pamphlet 4. 1969. 10, Suppl. 2, 5–32
129. Ibid, Pamphlet 5. 1969. 10, Suppl. 3, 5–52
130. Ibid, Pamphlet 6. 1970. 11, Suppl. 4, 5–32
131. Ellett, W. H., Callahan, A. B., Brownell, G. L. 1964. *Brit. J. Radiol.* 37:45–52
132. Harper, P. V. 1966. *Advan. Nucl. Med.* 1:8–14
133. Hendee, W. R. 1970. *Medical Radiation Physics*, Chicago: Yearbook Med. Pub. 599 pp.
134. Wrenn, McD. D. 1968. *Proc. First Int. Congr. Radiat. Protection*, 1966. 843–50 Oxford: Pergamon
135. Wrenn, McD. E., Howells, G. P., Hairr, L. M. *Health Phys.* In press
136. Wrenn, McD. E. 1967. *Health Phys.* 13:1075–82
137. Feige, Y., Gavron, A., Gross, J. 1969. *Israel Atomic Energy Comm. Res. Labs. Rep. IA-1199.* 243
138. Gillespie, F. C., Orr, J. S., Greig, W. R. 1970. *Brit. J. Radiol.* 43:40–47
139. Russell, W. L. 1970. In *Proc. IIth Int. Congr. Radiat. Res.*
140. National Council on Radiation Protection and Measurement. 1971. *Basic Radiation Protection Criteria.* NCRP Rep. 39, Washington, D.C.
141. Tamplin, A. R., Gofman, J. W. 1970. *Population Control through Nuclear Pollution.* Chicago: Nelson Hall 242 pp.
142. Gofman, J. W., Tamplin, A. R. 1971. *Health Phys.* 21:47–51

143. Tamplin, A. R., Gofman, J. W. 1970. Suppl. to Testimony presented at Hearings of the Joint Comm. on Atomic Energy 91st Congress of the U.S. on Studies of Radiation Effects on Humans. Document No. 2-8
144. Parker, H. M. 1967. See Ref. 48, 1241–50
145. Snyder, W. S. 1967. Ibid., p. 1256
146. Rosenblatt, L. S. 1973. See Ref. 5, 345–51
147. Rosenblatt, L. S., Hetherington, N. H., Goldman, M., Bustad, L. K. 1971. *Health Phys.* 21:869–75
148. [illegible] S., Ederer, F. 1958. *J. Chron. Dis.* 8:699–712
149. Goldman, M., Bustad, L. K. 1972. See Ref. 15, 1–16 pp.
150. Mole, R. 1969. See Ref. 4, 249–51
151. Tamplin, A. R., Gofman, G. W. 1970. JCAE Hearings, 91st Congr. Pt2 (Vol II) 2034–49
152. ICRP 1969. Publ. 14, *Radiosensitivity and Spatial Distribution of Dose.* Pergamon, 118 pp.
153. Blair, H. A. 1968. *Radiat. Res.* 34:501–22. Also Ref. 17, 203–12
154. Blair, H. A. 1973. *Health Phys.* In press
155. Albert, R. L., Newman, W., Altshuler, [illegible] 15:410–30
156. Brack, S. R., Sacramanno, C. 1968. *Health Phys.* [illegible]
157. Blanchard, R. L., Archer, V. L., [illegible] 16:583–96
158. Beasley, T. M., Held, [illegible] R. M. 1972. *Health Phys.* 2[illegible]
159. Persson, G., [illegible] *Health Phys.* 21:421[illegible]
160. Bergstrom, S. O. [illegible] *Phys.* 21:611–12
161. Brill, A. 1968. In *Radiol. Health Data & Reps.* 195–201 Rockville: Nat. Center for Radiol. Health
162. Comar, C. L. 1966. In *Radioecology and Human Diet* [illegible] Oxford: Pergamon
163. Forbes, G. B. [illegible] Part II, 207–14
164. Gruhn, A. 1971. *Health Phys.* [illegible]
165. [illegible] W. [illegible] 240 [illegible]
166. Karches, G. [illegible] *Health Phys.* [illegible]
167. Langford, J. C., [illegible] C. E. 1971. *Health Phys.* 21:[illegible]
168. Marei, A. E. et al 1972. *Health Phys.* 22:9–15
169. Pellerin, P., Remy, M. L., Ettel, P., Moroni, P. 1967. *Bull. I.N.S.E.R.M.* 22:357–82 France
170. Raymond, C. R., Fuechner, L. E. 1967. *Radiat. Res.* 32:5[illegible]–49
171. Shleien, B. 1970. *Health Phys.* 18:267–75
172. Bequ[illegible], H. et al 1971. *Environ. Physiol.* 1:37–50
173. Van Der Borght, O., Van Puymbroeck, O. 1970. *Health Phys.* 19:801–11
174. Auerbach, S. I. 1970. *Nuclear Power and the Public*, ed. Foreman, H., 2[illegible] Minneapolis: Univ. Minn. Press 273 pp.
175. Kirchmann, R., Colard, J., Fagniard, E. 1969. In *Symp. Int. Radioecologie* 677–88 Centre D'Etudes Nucleaires de Cadarache
176. Kirchmann, R., D'Souza, T. J. 1971. In Symp. Use of Isotopes and Radiation in Research on Soil-Plant Relationships 1–9 Vienna: IAEA SM-151/5
177. Van Den Hoek, J., Kirchman, R. J., Colard, J., Sprietsma, J. E. 1969. *Health Phys.* 17:691–700
178. Kitchings, J. T. III, Dunaway, P. B., Story, J. D. 1969. *Health Phys.* 17:265–77
179. Lengemann, F. W. 1970. *Zentralbl. Veterinarmedizin* 11:7[illegible]–87
180. IAEA, USAEC Proc. 1970. *Environmental Aspects of Nuclear Power Stations.* Vienna: IAEA STI/PUB 261, 970 pp.
181. Conard, R. A., Sutow, W. W., Colcock, B. P., Dobyns, B. M., Paglia, D. E. 1969. See Ref. 17, 325–3[illegible]
182. Tamplin, A. R., Fisher, H. L. 1966. Rep. UCRL-14707
183. Pendleton, R. C., Lloyd, R. P., Mays, C. W. 1963. *Science*, 141: 640–42
184. Hoffman, D. 1971. In *Annual Report,* [illegible] U.S.E.P.A., Washington, 251 pp.
185. *Nuclear Power and the Public* 1970. ed. Foreman, H. Minneapolis: Univ. Minn. Press 273 pp.
186. Sternglass, E. J. 1969. *Bull. Atomic Scientists* 25 [illegible] 29
187. Sternglass, E. J. 1969. [illegible] Ann. Meet. Health Phys. Soc. [illegible] Abstr. P[illegible]51
188. Sternglass, E. J. 1969. *Esquire.* Sept. 1969, 1a–d
189. Sternglass, E. J. 1969. See Ref. 12, pp. 693–717
190. Sternglass, E. J. 1970. Submitted

169. Pellerin, P., Remy, M. L., Ervet, P., Moroni, P. 1967. *Bull. I.N.S.E.R.M.T.* 22:357–82 France
170. Richmond, C. R., Furchner, J. E. 1967. *Radiat. Res.* 32:538–49
171. Shleien, B. 1970. *Health Phys.* 18:267–75
172. Beque, H. et al 1971. *Environ. Physiol.* 1:37–50
173. Van Der Borhgt, O., Van Puymbroeck, O. 1970. *Health Phys.* 19:801–11
174. Auerbach, S. J. 1970. *Nuclear Power and the Public*, ed. Foreman, H., 29–44 Mineapolis: Univ. Minn. Press 273 pp.
175. Kirchmann, R., Colard, J., Fagniard, E. 1969. In *Symp. Int. Radioecologie* 677–88 Centre D'Etudes Nucleaires de Cadarache
176. Kirchmann, R., D'Souza, T. J. 1971. In Symp. Use of Isotopes and Radiation in Research on Soil-Plant Relationships 1–9 Vienna: IAEA/SM–151/5
177. Van Den Hoek, J., Kirchman, R. J., Colard, J., Sprietsma, J. E. 1969. *Health Phys.* 17:691–700
178. Kitchings, J. T. III, Dunaway, P. B., Story, J. D. 1969. *Health Phys.* 17:265–77
179. Lengemann, F. W. 1970. *Zentralbl. Veterinarimedizin* 11:77–87
180. IAEA, USAEC Proc. 1971. *Environmental Aspects of Nuclear Power Stations.* Vienna: IAEA STI/PUB/261. 970 pp.
181. Conard, R. A., Sutow, W. W., Colcock, B. P., Dobyns, B. M., Paglia, D. E. 1969. See Ref. 17, 325–36
182. Tamplin, A. R., Fisher, H. L. 1966. Rep. UCRL-14707
183. Pendleton, R. C., Lloyd, R. P., Mays, C. W. 1963. *Science*, 141: 640–42
184. Hoffman, D. 1971. In *Annual Report*, 13–17, Twinbrook Res. Lab. U.S.E.P.A., Washington. 251 pp.
185. *Nuclear Power and the Public.* 1970. ed. Foreman, H. Minneapolis: Univ. Minn. Press 273 pp.
186. Sternglass, E. J. 1969. *Bull. Atomic Scientists* 25 10 p. 29
187. Sternglass, E. J. 1969. *14th Ann. Meet. Health Phys. Soc.* (Pittsburgh) Abstr. P 51
188. Sternglass, E. J. 1969. *Esquire* Sept. 1969, 1a–d
189. Sternglass, E. J. 1969. See Ref. pp. 693–717
190. Sternglass, E. J. 1970. Submitted testimony for *ASLB Hearing Shoreham Nucl. Power Sta.* No. 1, Docket 50–322
191. Sternglass, E. J. 1971. Testimony at *ASLB Hearing Davis-Besse Power Reactor*, Docket 50-346.
192. Sternglass, E. J. 1971. 16th Ann. Meet. on Health Phys. Soc. P 112 *Health Phys.* 21, Abstr. p. 57
193. Tompkins, E., Brown, M. L. 1969. *Bureau Radiol. Heath Tech. Rep.* DBE 69-2, 37 pp.
194. Hull, A. P., Shore, F. J. 1972. *Brookhaven Nat. Lab. Rep.* BNL 16513
195. Heller, M. P. 1970. *Am. Assoc. Physicians Med.* 4:24–27
196. Atomic Industrial Forum. 1971. "*INFO No. 29*", New York, 2 pp.
197. Hull, A. P. 1971. Presented at *6th Ann. Health Phys. Soc. Topical Symp.* Richland, Wash. BNL 16255
198. Tamplin, A. R. 1969. *Bull. Atomic Scientists* 25 10 23 pp.
199. Tamplin, A. R., Ricker, Y. 1969. *Rep. UCID-15506*, USAEC
200. Lindop, P. J., Rothblat, J. 1969. *Nature* 224:1257–60
201. Shaw, R. F., Smith, A. P. 1970. *Nature* 228:667–69
202. Greenwald, P., Kinch, S. 1969. *Rep. EXEP-690501.* USAEC
203. Weik, M. H. 1969. *JEAE, Hearings*, 91st Congress, Part I, 104–5
204. Fadeley, R. C. 1965. *J. Environ. Health* 27
205. Butler, J. C., III. Young, J. L. 1969. *Hearings, Joint Comm. Atomic Energy.* 91st Congress, Part I, 609–15
206. Stannard, J. N. 1973. Ref. 18, Chap. 15. In press
207. Romney, E. M., Mork, H. M., Larson, K. H. 1970. *Health Phys.* 19:487–91
208. Aberg, B., Hungate, F. P. ed. 1967. *Proc. Int. Symp. Stockholm* Pergamon, 1040 pp.
209. Morgan, K. Z., Struxness, E. G. 1971. See Ref. 180, 211–36
210. Morgan, K. Z. 1970. Lecture Int. Summer School Radiat. Protection. *Boris Kidric Inst. Nucl. Sci.* Cavtat. Yugoslavia 1–65 (obtained from author)
211. Morgan, K. Z. 1971. See Ref. 180, 301–13
212. Saiki, M., Umezu, T. 1965. *Proc. 2nd Int. Water Pollution* Res. Conf. Ciba. Japan 284–86. New York: Pergamon
213. National Academy of Sciences, USA. 1971. *Radioactivity in the Marine Environment.* Washington: NAS 272 pp.
214. Pruter, A. T., Alverson, D. L. Eds. 1972. *The Columbia River Estuary and Adjacent Ocean Waters.* Seattle: Univ. Wash. Press. 853 pp.
215. Feldt, W. 1970. In *Environmental Aspects of Nuclear Power Stations* 495–506 IAEA-SM-146/29
216. Seymour, A. H. 1970. In *Nuclear Power and the Environment*, Carson, M. W., Howlberg, W. A. Eds., Univ. Wisc. Proc. Conf. April 1970, XI-1-13, also XIV-10, 11
217. Polikarpov, G. G. 1966. *Radioecology of aquatic organisms.* Trans. Scripta Technica Ltd., ed. Schultz, V., Klement, A. W. Jr. New York: Reinhold
218. Bond, V. P., Feinendegen, L. E. 1966. *Health Phys.* 12:1007–20
219. Bond, V. P. 1971. See Ref. 180, 287–300
220. Dunster, H. J. ed. 1969 Progr. Rep. from ICRP. *Health Phys.* 17:389
221. Krisch, R. E., Zelle, M. R. 1969. *Advan. Radiat. Biol. III*, Augenstine Mason, Zelle, Eds. 177–213
222. Person, S. 1968. In *Biol. Effect Transmutation. Decay Incorp. Radioisotopes* 29–64. Vienna. IAEA
223. Cahill, D. F., Yuile, C. L. 1970. *Radiat. Res.* 44:727–37
224. Jacobs, D. G. 1968. *Sources of Tritium and its behavior upon release to the environment.* USAEC, Div. Tech. Info. 92 pp.
225. Tritium Symposium. 1971. Las Vegas, Nev. USPHS–USAEC