Mice, Men, and Fallout

The potential danger of strontium-90 is appraised on the basis of data from animal experiments.

Miriam P. Finkel

During the past few years a great deal of effort has been devoted to discovering how much radioactive debris has settled upon the earth and how much more will probably be added as a result of the nuclear weapons already tested and likely to be tested in the future. Even more effort has gone into researches to learn what proportion of this material will become incorporated in living things and how damaging it will be to plants, animals, and man. In addition to these studies, there have been many arm-chair predictions about the numbers of abnormal infants that will be produced each year, the numbers of people who will die of leukemia and bone tumors, and the numbers of years our lives will be shortened because of radioactive contamination. Some of these predictions have been made by well-known and respected scientists, physicians, and statesmen. Consequently, they have gained wide acceptance, and it is generally believed that thousands of individuals throughout the world are doomed because of the present level of radioactive fallout. It is appropriate at this time to examine critically the bases of these predictions and to analyze some of the available data relevant to the problem of the dangers of small amounts of radioactive materials.

It is not my purpose either to condemn future weapon testing or to nod approval to those who wish to try for bigger and better bombs. Problems in the realm of national policy and international relations must be judged by those who have access to the total necessary information, and the laboratory scientist is not likely to be included in this group. However, the laboratory scientist does have a duty to report the facts as he finds them, and there is a growing body of data upon which an evaluation of the potential hazards of radioactive fallout can be based.

It has been established beyond any possible doubt that irradiation, either from external sources or from radioisotopes within the body, can be dangerous. The manifestations and degree of damage depend upon many factors, such as the type and energy of the rays, the duration of exposure, and the portion of the body involved. In general terms, the major response of the total animal to high levels of irradiation is acute radiation disease and early death. At lower levels, tumor induction and shortening of life are the major signs of damage. In order to assess the dangers of fallout, it is necessary to know what happens at very, very low levels. Such information is completely lacking for man, and it is not easily obtained for experimental animals. Consequently, most predictions have been based upon extrapolations from the effects of higher levels of irradiation. These extrapolations involve two major assumptions. The first is that a linear relationship exists between the size of the dose and the magnitude of the response, so that only a segment of the curve requires experimental verification for accurate projecting of the entire curve. The second assumption is that no dose is so small that it has no effect. Once these premises have been accepted, the task becomes one of collecting all the cases displaying a particular result of irradiation, estimating the doses that produced these cases, and plotting response against dose in such a way that the origin of the extrapolated curve is zero on both scales, as has been done in Fig. 1, curve A. Curve B in Fig. 1 is a variation of curve A with the added complication of "background noise." However, curve C is an equally valid representation of these hypothetical data. Contrary to the other two curves, it assumes that a measureable response does not occur until a certain threshold dose has been exceeded.

The method of thoughtful guessing from a little knowledge is often the only possible approach to a problem, and the answers it provides are useful as long as they are qualified by the uncertainties of the assumptions that were made. However, the fact that many conclusions concerning the dangers of fallout are based upon incomplete data, partial curves, and speculations of this kind is often ignored.

There are other ways of estimating the human hazards of radioactive contamination. The usefulness of animal experimentation was recognized in the early days of the Manhattan Project (*1*), and such investigations have been under way since the products of nuclear fission first became available for biological study. Two major approaches have been used. The first takes advantage of the substantial fund of information on radium poisoning in man. It has assumed that the ratio of toxicities of any radioisotope relative to radium should be approximately the same in the experimental animal and in man if appropriate corrections for differences in retention, life span, size, and other factors are applied. The second approach has involved testing the same isotope in different species. The resulting correlations between toxicity and the various species characteristics then serve as a basis for extrapolation to an animal such as man.

Unfortunately, investigations of the long-term effects of small amounts of toxic agents require a great deal of time, the minimum interval for a complete study being the length of life of the longest survivor. Definitive answers from animal experimentation on fission-product toxicity are not yet available, but the data that have been accumulated during the past 14 years provide a reasonably sound basis for a few predictions about the dangers of human contamination with many radioactive materials. Since the greatest interest now centers around strontium-90 fallout from nuclear weapons, the remainder of this article deals with some of the laboratory data on the toxicity of this isotope. These studies (*2*) are concerned with the effects upon the exposed generation only.

Experimental Rationale and Methods

The most useful criteria of radiation damage to the mammalian organism as a whole are decrease in life span and increase in the incidence of certain tumors. These changes can be accurately meas-

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ured and evaluated only when large populations are observed during their entire life span. The laboratory mouse is well suited to this type of experimentation because hundreds of animals can be maintained in a relatively small space, and strains with a high degree of genetic and physiologic uniformity can be obtained in large numbers. In addition, since the average mouse lives less than two years, mortality and morbidity data become available within a reasonably short time. However, some of the same characteristics that make the mouse so useful for long-term radiotoxicity studies render direct extrapolation of the data to man impossible. Consequently, information on larger and longer-lived animals is essential to bridge the extreme differences that exist between mouse and man.

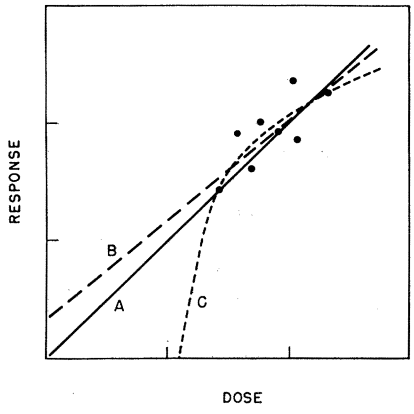

Fig. 1. Possible extrapolations from hypothetical data. (Curve A) This method, the one usually employed, assumes that the origin of the dose-response curve is at zero on both the ordinate and the abcissa. (Curve B) This method also assumes that there is no threshold, but it adds a normal background incidence that prevents an origin at zero on the ordinate. (Curve C) This is an equally acceptable extrapolation from the meager data presented, which assumes that there is a threshold dose that must be exceeded before the response is manifest.

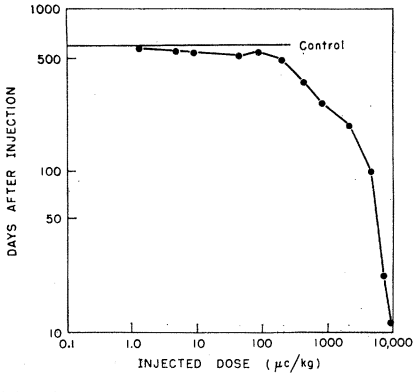

Fig. 2. Average survival time, or life expectancy at the time of injection, plotted as a function or dose.

Human contamination with radiostrontium will occur primarily through ingestion, but the effective dose at low levels is expected to be that which becomes incorporated in the skeleton rather than that which passes through the gastrointestinal tract. Therefore, difficulties in the general application of animal data as a result of interspecific differences in absorption characteristics can be minimized by administering the isotope intravenously. Appropriate corrections based upon absorption factors can then be applied when particular exposure situations are being evaluated. Another difference between human contamination from fallout and animal experimentation with intravenous injection is the length of time during which exposure continues. In the former case the body burden is increased gradually; in the latter case the initial amount of strontium-90 in the body may exceed the amount eventually retained in the skeleton by a factor of 10. Prolonged exposure also leads to a more uniform distribution of radiostrontium within the bones. The effects of both the high initial dose rate and the degree of uniformity of deposition are currently being studied in experiments involving several fractionated dose regimens.

Briefly, then, the mouse is providing basic, statistically reliable information on decrease in life span and increase in the incidence of certain tumors after a single, intravenous injection of strontium-90. These data are being supplemented by mouse experiments in which the route and duration of exposure are varied and by experiments on larger, longer-lived animals, such as cats and dogs.

The plan of the strontium-90 toxicity experiment is given in Table 1. At high levels only a few animals were used, because the effects were expected to appear rapidly and to be unequivocal; at low levels many animals were required, because the effects were expected to appear late, to be less diagnostic of radiation damage, and to require statistical testing. It was intended that the highest dose should reach or exceed the amount necessary to kill 50 percent of the population in 30 days and that the lowest dose should be so low that the treated animals would be indistinguishable from the controls. The lowest injected dose, 1.3 μc/kg, resulted in a body burden of approximately 0.14 μc/kg at 600 days. This is roughly equivalent to 10 μc in a 70-kg man, or to ten times the currently accepted maximum permissible level for personnel engaged in atomic energy work and to 100 times the level set for the general population (*3*).

Young adult female mice (strain CF No. 1) were randomized into the permanent experimental groups 1 week before injection. Dosage was based upon the average weight of the entire population. Postinjection routine included daily observation of all animals and the sacrifice of moribund mice with Nembutal after a peripheral blood sample had been withdrawn. Autopsy was followed by x-ray examination of the entire skeleton and by histologic study of a number of tissues. All organs with grossly visible lesions and all bones with roentgenographically detected abnormalities were added to the tissues regularly taken for histopathology.

Results

In Fig. 2 the average survival time has been plotted against dose on a double-logarithmic grid. At dosages of from 1.3 through 88 μc/kg, the treated animals died, on the average, a little sooner than the control animals, but their deaths were not associated obviously with any particular disease. At dosages of from 200 through 2200 μc/kg, the primary cause of death was neoplastic disease; at higher dosages it was subacute and acute irradiation disease. The values at 1.3, 4.5, and 8.9 μc/kg are not significantly different from the control value. It was calculated that a difference as small as that noted at the lowest dose would be significant at the 1-percent confidence

Table 1. Plan of the strontium-90 toxicity experiment. Female mice, strain CF No. 1, received a single, intravenous injection of an isotonic equilibrium mixture of strontium-90 and yttrium-90 chloride, at *p*H 5 to 6, when they were approximately 70 days old.

Group	No. of animals	Injected dose (μc/kg)	Body burden* (μc/kg)
1	15	9330	1026
2	30	7000	770
3	45	4500	495
4	30	2200	242
5	45	880	97
6	45	440	48
7	60	200	22
8	75	88	9.7
9	90	44	4.8
10	105	8.9	1.0
11	120	4.5	0.5
12	150	1.3	0.14
Control	150	0	0

* The body-burden figures are based upon 11-percent retention at 600 days after injection (*7*), which was the average survival time of the control mice.

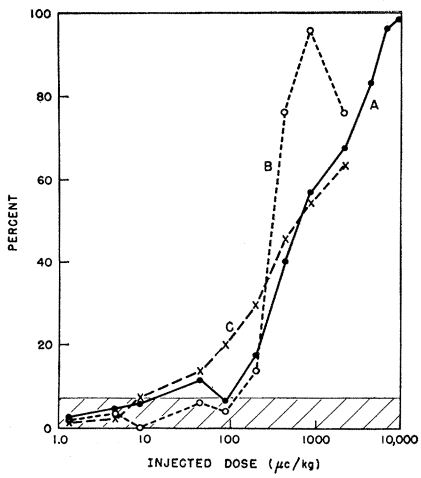

Fig. 3. Effect of strontium-90 on life expectancy and on incidence of tumors of bone and blood-forming tissues. The points within the shaded area are not statistically significantly different from the control values; the shaded area represents nonsignificance at the 10-percent probability level or higher by the *t* test. (Curve A) Percentage decrease in average survival time (life expectancy at start of experiment) compared with average survival time of the controls. (Curve B) incidence of animals with osteogenic sarcomas among 150-day survivors. The incidence among the control population was 2 percent. (Curve C) Percentage decrease in time to a 20-percent incidence of reticular tissue tumors compared with the 20-percent incidence time of the controls.

level if it had been based upon 1393 treated animals compared with the same number of controls, or almost ten times as many mice as were used to establish these points. This calculation, which is based on the assumption of unchanged variability in a larger population, emphasizes one reason why definitive data at very low levels are difficult to obtain. The lowest injected dose that resulted in a statistically significant decrease in life span was 44 μc/kg. These mice had a retained dose of approximately 5 μc/kg, which corresponds to 350 μc per 70-kg man, or to 350 times the maximum permissible body burden for people engaged in atomic energy work and to 3500 times the level set for the general population.

In Fig. 3, curve A illustrates the percentage decrease in average survival time, compared with the average survival time of the control population, plotted against the logarithm of the dose. Even though the animals that received 44 μc/kg showed a statistically significant decrease in life span, those that received 88 μc/kg did not. This peculiar result was due in part to the fact that the two longest survivors in the entire experiment belonged to this group.

Various tumors that might be attributed to strontium-90 appeared in and around bone. There was a pronounced association between dose and both osteogenic sarcomas and hemangioendotheliomas of bone marrow, and there was a suggested association between dose and epidermoid carcinomas of the oral cavity. Fibrosarcomas adjacent to bone and benign skeletal tumors were not influenced by radiostrontium, except insofar as their total incidence was lower at levels that decreased survival time substantially. The proportions of animals that survived the latent period of 150 days and then died with osteogenic sarcomas are shown in Fig. 3, curve B. There were three osteogenic sarcomas among the control mice, an incidence of 2 percent. The lowest injected dose that resulted in a significantly higher number of osteogenic sarcomas was 200 μc/kg. This dose is almost five times larger than the lowest level that resulted in a significant difference in survival. At the next lower dose (88 μc/kg) there were twice as many tumors as in the control group, but the probability that this was due to chance was 30 to 50 percent, as determined by the *t* test. At 44 μc/kg there were three times as many tumors, with a probability of chance occurrence of 20 to 30 percent.

Other neoplasms occurring in the mouse that are influenced by irradiation are those that show certain similarities to the leukemias of man. This group of tumors has been designated by a variety of names, among which are mouse leukemias, lymphomas, lymphoid tumors, thymic tumors, and reticular tissue tumors. They involve the blood-forming tissues, and they arise primarily in the lymph nodes, thymus, spleen, and bone marrow. Although the total incidence of these tumors was not markedly influenced by dose in this experiment, they appeared much earlier among the animals that had received 88 μc/kg or more. Therefore, the data were examined further for evidence of a relationship between dose and time of death with reticular tissue tumors. In curve C, Fig. 3, the percentage decrease in the number of days from injection to the time when 20 percent of the population had died with tumors of the blood-forming tissues is plotted against the logarithm of the dose. The control animals reached a 20-percent incidence 565 days after the beginning of the experiment. The two lowest points on the curve are not significantly different from the control value; the point at 8.9 μc/kg is significant at the 1-percent confidence level. This dose is one-fifth of the lowest dose that produced a significant difference in life span. It resulted in a body burden of approximately 1 μc/kg, which is roughly equivalent to 70 μc/man, or to 70 and 700 times the currently accepted maximum permissible levels for occupational and nonoccupational exposure, respectively.

Linearity and Threshold

In spite of the many differences that exist between mouse and man, it is most likely that the general laws of radiotoxicity that apply to the mouse also apply to man. The experimental data just presented provide the best current information on the shape and origin of the dose-response curve as measured in the total mammalian organism. Since the greatest interest concerns low amounts of irradiation, the data from only the five lowest dose levels have been replotted in Fig. 4 on a rectangular grid in place of the semilogarithmic grid used in Fig. 3. The latter was necessary in order to include the large range of doses in the complete experiment; the former is required for determinations of linearity.

None of the curves in Fig. 4 can be described by a simple linear function. Although the values of the four lowest dosage groups in curve A (reduction in life span) suggest a direct relationship between dose and response, it is not a linear one. Since three of these values

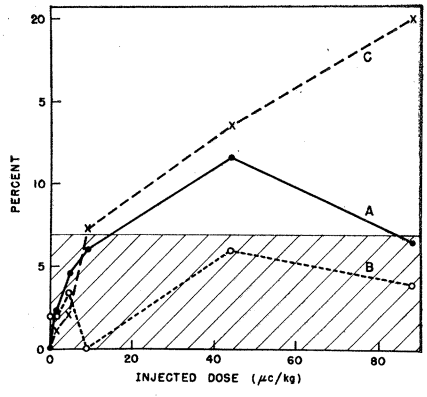

Fig. 4. The relationship of dose and response at low levels. Values above the shaded area are significantly different from the control values. Within the shaded area the probability is 10 percent or greater that there is no difference between the experimental and the control values. (Curve A) Percentage reduction in average survival time. (Curve B) Incidence of animals with osteogenic sarcomas among 150-day survivors. (Curve C) Percentage decrease in time to a 20-percent incidence of reticular tissue tumors.

are not significantly different from the control value, a threshold for the life-shortening effect may lie between 4.5 and 44 μc/kg. However, since the values for 1.3, 4.5, and 8.9 μc/kg do lie along a straight line when plotted semilogarithmically (Fig. 3), it may be argued that they represent true departures from the control value. An extension of this straight line crosses the control value at 0.4 μc/kg.

The incidence of osteogenic sarcomas at these five lowest levels did not extend beyond the statistical limits of the control range, and the data show no trend and no indication of any relationship between dose and response (Fig. 4, curve B). Therefore, a threshold for the induction of these neoplasms in female mice, strain CF No. 1, might lie between 88 and 200 μc/kg. However, since there were two and three times as many tumors among the animals that received 88 and 44 μc/kg, respectively, as there were among the controls, a threshold may actually lie below the latter dose. There were not enough animals at these levels to permit statistical verification of differences as small as those observed.

The three lowest points of the reticular tumor curve that were significantly different from the control value (at 8.9, 44, and 88 μc/kg) do lie along a straight line (Fig. 4, curve C). The values of the two lowest dose levels (1.3 and 4.5 μc/kg), which did not differ significantly from the control value, were examined to determine whether they fell within the statistical range of an extension of this straight line. They were found to lie so far beyond this range that there was no serious likelihood that they belonged to it. If these data do not demonstrate that a threshold dose must be exceeded before there is a measurable change in the course of tumors of the blood-forming tissues in CF No. 1 female mice, they at least show that the dose-response curve is not linear.

Extrapolation to Man

Since it has not been possible to demonstrate a linear relationship between dose and response, the use of straight-line extrapolations from fragmentary human data may be very misleading. In addition, the evidence that there might be a threshold, and consequently a true maximum "indifference dose" for pathologic change as measured in the total animal, raises serious objection to the practice of extending such lines to an origin at zero response and zero dose.

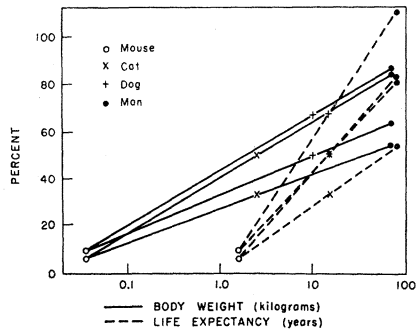

Fig. 5. Estimation of the incidence of osteogenic sarcomas and hemangioendotheliomas of bone marrow in man after an injection of 150 μc of strontium-90 per kilogram. The extrapolations are based upon current data involving mice, cats, and dogs, and they assume a relationship between tumor incidence and body size or life span.

Consequently, other methods of estimating the human hazard from strontium-90 must be used.

Radium method. Comparisons of toxicity ratios with radium as the common denominator between experimental animals and man can be applied as follows. The lowest injected doses that increased the incidence of osteogenic sarcomas in CF No. 1 female mice were 44 μc of strontium-90 and 1.2 μc of radium-226 per kilogram (*4*). This dose of strontium-90 did not significantly increase the incidence of bone tumors related to the controls when evaluated by the *t* test, but since it resulted in the appearance of bone tumors among 6 percent of the treated animals as compared to an incidence of 2 percent among the controls, it was chosen as a probable minimum effective dose. These strontium and radium doses have a ratio of 37 to 1. The largest injected doses tested that did not increase the incidence of osteogenic sarcomas were 8.9 μc of strontium-90 and 0.6 μc of radium-226 per kilogram. This is a ratio of 15 to 1. Thus, at levels in the region of minimum effect, radium is probably somewhere between 15 and 37 times as effectual as strontium-90. In a recently reported series of radium-containing human patients, among those who were probably exposed to relatively pure radium-226 there was one individual with a body burden of 0.4 μc who had minimal but positive roentgenographic evidence of radiation changes (*5*). There were no positive cases at lower levels among those with body burdens uncontaminated with mesothorium, but most of the patients with from 0.5 to 1.0 μc showed similar, minimal lesions. If 0.4 μc of radium represents a dose of minimum effect in man, application of the factors 15 and 37, derived above, results in the estimate that the minimum effective dose of strontium-90 in man is a body burden of from 6 to 15 μc.

The comparative toxicology method. Another approach involves extending the data obtained from a relatively large number of mice, through data obtained from fewer but larger and longer-lived animals, to man. Since the major damage from strontium-90 is due to the energetic beta rays of its yttrium-90 daughter, and since a large proportion of this energy is wasted in an animal as small as a mouse, it is expected that the tumor-producing efficiency of strontium-90 should increase as the size of the animal increases.

The only experiments involving the toxicity of strontium-90 in larger animals that have progressed far enough to be useful for this purpose are two studies including six dogs and six cats that lived more than five months after receiving 150 μc/kg by a single, intravenous injection. Three of the five dogs that have died had osteogenic sarcomas; the sixth is still alive and free of roentgenographic evidence of bone disease. Thus, the final incidence of malignant bone tumors will be 50 or 67 percent. The incidence among mice at the same injected dosage can be estimated to exceed the incidence among the control population by 9 percent. This figure is based upon interpolation between the results obtained at 88 and 200 μc/kg (Fig. 3). When these percentages are plotted against the logarithm of body weight (a 35-g mouse and a 10-kg dog) and extrapolated to a 70-kg man, tumor incidences of 63 and 87 percent are obtained (Fig. 5). When they are plotted against the logarithm of life expectancy (1.6 years for the mouse, 15 years for the dog, and 80 years for man), extrapolation to man gives 80 and 110 percent. These incidences divided by the 9 percent established for the mouse give quotients ranging from 7 to 12. Therefore, strontium-90 might be from 7 to 12 times more effective in man than in mice.

Of the six cats that lived beyond the latent period for tumor induction, two died with osteolytic tumors that have been tentatively diagnosed as hemangioendotheliomas of bone, one died with roentgenographic evidence of the same disease, as yet unverified histologically, and three died free of skeletal malignancies. The incidence of hemangioendotheliomas among mice at 150 μc/kg would be expected to exceed the inci-

dence among the control population by 6 percent on the basis of the incidences at 88 and 200 μc/kg (*6*). The projected incidences for man based upon cats weighing 2.5 kg and having a life expectancy of 15 years range from 54 to 84 percent (Fig. 5). These incidences divided by the 6 percent established for the mouse give quotients of from 9 to 14.

These extrapolations from mice through dogs and cats suggest that strontium-90 is from 7 to 14 times as toxic in man as in mice. The lowest dose that could be shown to have any effect in the mouse was 8.9 μc/kg, which decreased the time interval to the appearance of reticular tissue tumors. This is equivalent to 1 μc retained per kilogram, or to a body burden of 70 μc per 70-kg man. Dividing this dose by the mouse-to-man factor of from 7 to 14 leads to the estimate that the minimum effective dose in man may be a body burden of from 5 to 10 μc of strontium-90.

Danger from Present Fallout Contamination

Perhaps it is merely coincidence that the 6 to 15 μc estimated for the minimum effective dose in man based on the radium method of extrapolation and the 5 to 10 μc estimated from the mouse, dog, and cat data are so similar. In spite of their very tentative nature, these calculations are presented here to illustrate how experimental animal data may be used. In the next few years there should be additional information on radium toxicity in man, since several hundred persons with a possible radium burden are currently under investigation. Consequently, the level of minimum effect will be known with greater exactness. Also, the dog experiments now in progress in several laboratories should provide information over a range of doses so that extrapolations from mouse through dog to man will be possible at more than one level.

The lowest prediction of a harmful dose to man that can be made from the present data attaches significance to the statistically insignificant differences in average survival time at the lowest doses in the mouse experiment. The line passing through these points intersects the control value at an injected dose of 0.4 μc/kg. This dose is equivalent to a retained dose in mice at 600 days of 0.044 μc/kg, or to a body burden in a 70-kg man of 3.08 μc. If the life-shortening factor in going from mouse to man is as great as the estimated tumor-inducing factor—an unlikely assumption for several reasons—a threshold value for man would lie between 0.22 and 0.44 μc of strontium-90. A more likely value is one that lies between 5 and 15 μc, as discussed above. In any case, the present contamination with strontium-90 from fallout is so very much lower than any of these levels that it is extremely unlikely to induce even one bone tumor or one case of leukemia.

References and Notes

1. The Manhattan Project, which developed the atomic bomb, was terminated in 1947. The biological work in progress at that time was continued without interruption under the sponsorship of the newly created Atomic Energy Commission.
2. This work was performed under the auspices of the U.S. Atomic Energy Commission. The views expressed are my own and do not necessarily reflect those of the Biological and Medical Research Division of Argonne National Laboratory.
3. *Natl. Bur. Standards (U.S.) Handbook No. 52* (U.S. Dept. Commerce, Washington, D.C., 1953).
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5. W. B. Looney, R. J. Hasterlik, A. M. Brues, E. Skirmont, *Am. J. Roentgenol. Radium Therapy* **73**, 1006 (1955).
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7. M. P. Finkel, B. J. Tellekson, J. Lestina, B. O. Biskis, *Argonne Natl. Lab. Biol. and Med. Research Div. Semiann. Rept. No. ANL-5732* (1957), p. 21.

George Sarton, Historian of Science and New Humanist

"Am flying to-morrow morning to Montreal. Vale *G S*" wrote George Sarton on 21 March 1956. He was scheduled to give a lecture in Montreal on 22 March but became ill on the way to the airport and died that day in his Cambridge, Massachusetts, home. Thus, while he was still active and mentally young, the life on earth of this great historian of science came to an end—a life which had begun 72 years earlier, on 31 August 1884 in Ghent, and which had bridged two continents and more, both physically and spiritually.

Death has not ended Sarton's influence. He had continually emphasized the idea that the history of science is not the sum of the histories of the separate sciences but rather their integration, that it is itself a specialty built on a thorough understanding of the methods of science and of history, and that it requires more than the leisure hours of capable scientists or of scholarly historians. He frequently referred to it as a new discipline, and he established it as such in the United States. It bears his mark. Thanks to his persistent pleas, expressed in letters, talks, and published works, and the interest he stimulated, there are now chairs of the history of science and courses or series of courses in that subject in many of our leading universities. Moreover, scholars the world over consult his numerous publications, of which *Isis* and the *Introduction to the History of Science* are the best known (*1*).

George Sarton's early education was obtained first at the Athénée in Ghent and then at that in Chimay. He attended the University of Ghent in the department of philosophy, studied by himself for a year, and returned to the university to study the natural sciences, chemistry and crystallography, and mathematics, in which he received a doctorate in 1911 (*2*).

In 1908 he wrote a chemical memoir (*3*) which gained for him a gold medal offered by the four Belgian universities and a silver laurel branch from the city of Ghent. In these early years he also wrote romantic books and poems (*4*), an exercise which contributed to the development of his eminently readable prose.

Influenced by the writings of Comte, Tannery, Duhem, Poincaré, and others, while he studied pure science, Sarton grew increasingly more interested in the history and philosophy of science. He came to believe that the basis of all