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THE TIME FACTOR IN CARCINOGENESIS

THE 1977 SIEVERT LECTURE*

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MAY I first express my appreciation of the great honor you have done me in choosing me as the second recipient of the Sievert Award with its accompanying invitation to deliver a lecture in memory of Rolf Sievert. I am deeply conscious of the distinction, and even puzzled at being thus chosen from among so many who have contributed to the development of the art and science of radiation protection. But perhaps you were influenced by the knowledge that Sievert and I were friends for some forty years, though I am not sure that this does not make my task heavier rather than lighter. As my distinguished predecessor, Dr. Bo Lindell, remarked (Li76), it is impossible to recreate in a few words the personality of Rolf Sievert, that genial but demanding giant. Rolf and I were first acquainted in the 1920's. Let me try to set the scene as I remember it.

Sievert was a member of a very remarkable group of pioneers led by Gösta Forssell, a distinguished radiologist moving in the highest social circles and undeniably the head of the Swedish medical profession. With him were Dr. Heyman, a gynecologist whose work on the radium treatment of cancer of the cervix uteri was revolutionizing gynecological practice, Dr. Berven, a distinguished radiotherapist, and the young Rolf Sievert, highly gifted and clearly destined to leadership among the small group of physicists who had ventured into this medical field. This was a time of great hope and optimism in radiation therapy. Here in Paris, at the Fondation Curie, another extraordinary group, inspired by Madame Curie and led by Professor Claude Regaud and his brilliant colleague Lacassagne, were carrying the subject forward from a very different point of view. The Swedish group was particularly strong in the physical and mathematical as well as the clinical sciences; the French school, it seemed, only secondarily interested in the physical aspects, concentrating their genius (for it was no less) on biological research as revealed, for example, in their "Radiophysiologie et Radiothérapie" (Re27). There were at this time no nationally or internationally agreed units of dose or methods of measurement, and few quantitative studies of the distribution of radiation around radioactive sources of medical interest, meaning in those days "radium needles" inserted into tissues or body cavities.

In 1921 Sievert published his first important work, "Die Intensitätsverteilung der primären γ-Strahlung in der Nähe medizinischer Radiumpräparate" (Si21). Its theoretical and practical importance was at once recognized and the mathematical skill obvious, but controversy was raised. Was the "intensity of primary gamma rays" what mattered in a scattering medium which itself contributed significantly to dose? I remember this discussion very well, being myself a pupil of Friedrich then much concerned with secondary scattered radiation and its significance. Sievert himself, of course, recognized the complexity of the problems and in 1923 pub-

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lished a second paper on "Secondary rays in radium therapeutics" (Si23) in which, as I reread it, I realize how close he came to anticipating me by some twenty years on reciprocity theorems! Sievert's original paper (Si21), we must remember, was two years earlier than the discovery of the Compton effect and its resulting recoil electrons (1922–1923). We were still groping to find a physical agent capable of causing the undoubted biological effects of gamma rays. Sievert's papers inspired a new literature and approach to radiation distribution problems. They also, as an interesting sideline, earned him the distinction of being the only medical physicist to give his name to a definite integral. Rolf calculated tables of its values "by graphical methods", a formidable task. We now know that the integral is related to the error function, exponential integrals, and certain integrals of Bessel functions. Though tables of values are now available to six significant figures, I have yet to find an error in Rolf's original values!

It would be tedious and pointless to try to discuss Sievert's publications in detail. They should be savored in the original, so I will mention only two or three that are particularly outstanding. His first paper on protection, "Einige untersuchungen über vorichtungen zum schutz gegen röntgenstrahlen" (Si25), in which he became concerned about secondary rays from walls, floor, and ceiling, seems to have been in 1925. From this time onwards a stream of investigations into protection and standardization problems may be traced.

In 1932 he published one of the masterpieces of radiological literature, his Supplement 14 to *Acta Radiologica*, "Eine methode zur messung von röntgen-, radium- und ultrastrahlung nebst einige untersuchungen über die anwendbarkeit derselben in der physik und der medizin" (Si32). "The method" is, of course, the use of small condenser chambers. This work, I think, best illustrates his essential characteristics. The thorough theoretical grasp of the problem, the imaginative ingenuity, the outstanding experimental competence backed by the extremely high standards of technical execution we have come to expect from our Swedish colleagues, are here shown at their best. To the end of his life Rolf loved imagining and constructing with his own hands delicate and beautiful instruments, sometimes perhaps almost too delicate as were condenser chambers in the hands of less skilfull workers. Which moves me to say that, like all the best scientists I have known, Rolf Sievert was essentially an artist subject to the vagaries and vacillations of inspiration. This artistic trait appeared in a more conventional artistic form in, for example, his interest in and designs of objects in glass made under his direction or in his love of music, particularly that of J. S. Bach. He was an enthusiastic and competent organist who built for himself a small "chapel" with an organ, on the shores of a beautiful lake in his country estate in Southern Sweden. Those of us who were privileged to stay at his apartment in the Karolinska will remember, too, the delightful artistry of those rooms and the generous care for our comfort. Generosity was, indeed, an outstanding characteristic. He loved good living himself and loved providing and sharing it with his friends. Sometimes meals as, for example, feasts of crayfish in the true Swedish tradition, became something of a challenge!

But let us return to his national and international interests and achievements. He was early a member of the International X-ray Units Committee as well as the Protection Committee of the International Congresses of Radiology following the very successful meeting in Stockholm in 1928, at which the roentgen was adopted as unit of dose. His department became the central standardizing laboratory in Sweden.

After the War, at the Radiological Congress in London in 1950, the international radiological organizations had to be completely reconstructed, sometimes in the face of considerable international tension. Sievert was a tower of strength. His personality and scientific standing, coupled with the political position of Sweden, were of great importance and it was inevitable that he should be a member of the newly formed International Commissions of Protection and

Units, with greatly increased public responsibilities, scope, and independence of status. A little later the problems of environmental monitoring were uppermost in many minds, and Sievert was responsible in Sweden itself for the setting up of an appropriate organization and for developing with his usual skill high pressure ionisation systems. I remember well many earnest conversations with him on the need for detailed legislation of which he had great experience, its form and content. I think I personally preferred less detailed and less formal legal arrangements than he did, but time has shown the wisdom or at least necessity of his approach, and it was always a delight to discuss these matters with one so friendly, wise, sincere and helpful. My recollection is that he said relatively little in formal committees but his interventions were very effective and massive, and he usually had his way! Perhaps our closest personal association came via the United Nations, both its Scientific Committee and Peaceful Uses Conference as well as the International Commission on Radiological Protection (ICRP). We were, indeed, both of us, members of a Committee of the old League of Nations (concerned with ionizing radiations) which met in 1939.

Sievert was very seriously concerned with the problems of international relationships, "fallout," and population exposure. However, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) quickly established itself and played a major rôle in the collection of universally acceptable data and in setting guidelines. Sievert certainly contributed greatly to the formation, efficacy, and clear discussions of that Committee and its speed of working. I remember Dag Hammershöld, then Secretary-General of the United Nations, expressing to me his astonishment at the speed with which the Committee had got down to work. UN officials had allowed us ten days of "preliminary discussion on procedure," yet we actually started serious scientific discussion on the first afternoon. Some of my most vivid memories of Sievert are of wandering with him along the slippery and interminable corridors of the Palais des Nations in Geneva or the palm-laden foyers of the UN Headquarters in New York, while he dissected with insight and humor the previous hours discussion. Perhaps you will forgive my immodesty if I show a photograph (Fig. 1) taken in Geneva, a rather less formal but more characteristic picture of Rolf than that in *Health Physics* of the learned Chairman of ICRP.

Sievert certainly was a powerful Chairman of ICRP and could look forbidding and register annoyance quite distinctly and unmistakably, but ordinarily he was extremely persuasive and persistent and carried his Committee with him by weight of experience and knowledge.

But I must conclude my sketch of Rolf. I would like to convey something of his greatness, something of his lovable humanity and generosity as well as overpowering intellect and artistic sensitivity. Whatever else he was, he was no Standard Man (a concept I suspect he would have rather despised) either in body or mind. I see him now, a towering mass of humanity, overflowing his chair in a way I have only ever seen equaled by one man, the poet G. K. Chesterton. Rolf, like all good-natured men with a marked sense of humor, laughed at and enjoyed his own jokes. I would sometimes try to say a few words in Swedish. The great mass would begin to oscillate while a deep gurgle resolved itself into words—"Eet zounds zo funnee when you say eet!" Which I am sure it did!

Rolf Sievert was one of the giants of radiological science, including protection. His energy, flow of ideas, enthusiasm, and immense knowledge were phenomenal. His level-headed judgments were also bastions of common sense against extreme decisions, whether of policy or permissible levels.

One other contribution I must mention in a very different field. There was at one period very considerable anxiety about money to carry on the work of the Protection Commission and here, too, his financial status and acumen were of great value. I remember well going with him in New York to open negotiations with the Ford Foundation and marveling at his persuasive powers and skill in this field too.

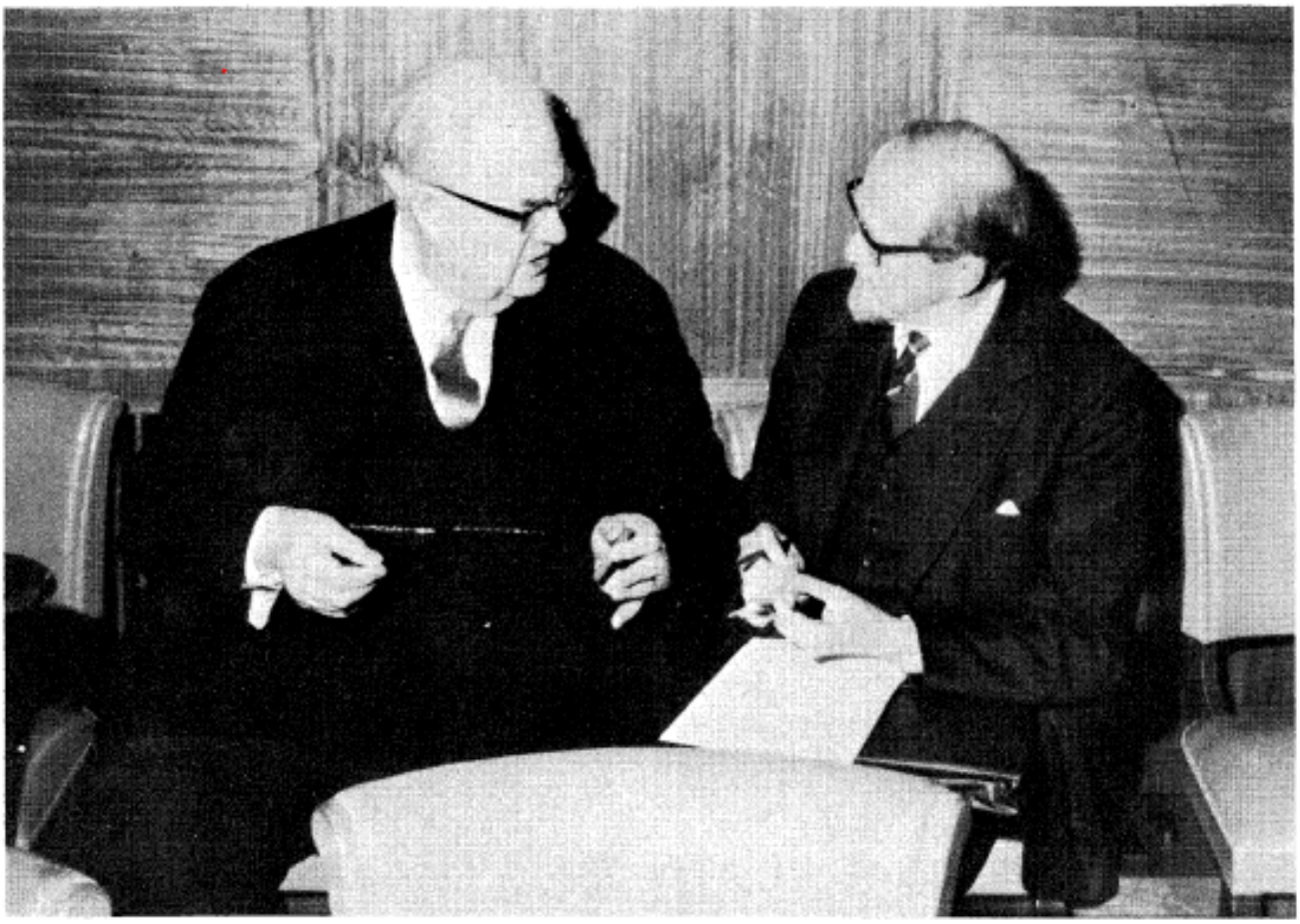

FIG. 1. Rolf Sievert and Val Mayneord.

He enjoyed his powers and eminence but apparently had little idea of the outstanding quality of his scientific achievements and as a result was extremely modest about them. He need not have been, for the spirit remains even though the precise technologies of ionization chambers and mechanical electrometers have largely gone.

In the year 1941 Sievert published in *Acta Radiologica* a fascinating theoretical paper, "Zur theoretisch-mathematischen Behandlung des Problems der biologischen Strahlenwirkung" (Si41). In it he discussed, in his usual masterly way, a very general mathematical theory of the action of radiation on the living cell in terms of the deviations from their normal values of concentrations of essential cell ingredients under irradiation at different dose rates. Many times he expressed to me his concern lest the very high dose rates in diagnostic radiology might be particularly hazardous. Sievert introduced the concept of a "latent period" depending on radiosensitivity and the presence and speed of reconstitution of reserves in the cell of relevant materials. Many simplifying assumptions must be made, but Sievert derived a series of difference or differential equations which, though they could not be solved generally analytically, were treated graphically. He applied this theory to the extensive series of results by his colleague Arne Forssberg on *Phycomyces* and *Drosophila* eggs. Sievert opens the paper with an eloquent encouragement to the mathematical biologist. Translating freely, "Human capacity to judge of the logical consequences of many factors acting together is very limited, and it is often of the greatest importance to translate the observations into mathematical language and to use mathematical methods rather than attempt to proceed directly". True, his paper ends with words of warning, but I would like to use his in-

vocation as an excuse for the rest of this lecture, building on the foundations he laid. I wish I could think my superstructure as solid as his foundations!

It is universally agreed that one of the most important late effects of irradiation is the induction of tumors. As you are very well aware, much effort has been expended in attempts to correlate biological effect with dose, often the total number of tumors observed in a population of animals with dose to relevant tissues or cells. The resulting dose–response curve is then analysed in an attempt to throw light on essential mechanisms or to support estimates of effects to be expected in a given dose range.

An important feature of carcinogensis is the long so-called "latent period" between the application of the carcinogen and the observation of the tumor, this time interval usually being greater the smaller the dose of the agent, whether physical or chemical. What precisely is happening in that latent period we do not know, but much evidence from pathology, cytology, and many other fields suggests the occurrence of a series of events, mostly moving towards increasing abnormality and heterogeneity of structure of cells and tissues until limited by abnormality so great as to lead to cell "death" or, rarely, capacity for increased and barely controlled cell division. "Latent" is a misleading term if it suggests "inactivity".

This is a vast subject and I can only indicate the briefest outline. Suffice it that, as we look at the detail, we seem to be forced to recognize an element of chance in the processes. In the jargon of probability theory, each cell is a "trial", each cellular life history a "realization" of a Random Walk or Markov chain, each tumor an outcome of complex interplay of inter- and intra-cellular events. Probably no two tumors are genetically, cytologically, or immunologically precisely identical, yet from what miracles of precise mechanism they arose! Radiation introduces confusion, "genetic noise". In a deterministic sense, carcinogenic agents, including radiation, do not "cause" cancer. They modify the probability of its later occurrence, often increasing that probability, sometimes decreasing it, altering the time scale of the events.

The idea that the essential action of radiation is to confer a probability of cancer in the future is not new. In 1949 Austin Brues (Br49) analysed the rate of appearance of osteosarcomas as a function of time and radioactive intake of a group of several thousand mice given monthly injections of the beta emitter ^{89}Sr. He concluded, "that each quantity of absorbed radiation confers on the tissue absorbing it a probability (per unit time) of tumor formation which is without limit in time once the latent period is passed; thus, the daily tumor morbidity will continually increase so long as further radiation occurs". Figure 2 shows Brues's results for the variation with time of the probability per animal per day of the appearance of a tumor. We note that the larger the dose, the shorter the time.

In an admirable and important recent paper Marshall and Groer (Mar75) modified the hypothesis by considering the effects of cell killing, thus limiting the time and number of cells over which the probability is significant. Marinelli (Ma71) earlier argued for risk per unit dose of alpha radiation chronically delivered remaining constant in time.

During the last three years or so Dr. Roger Clarke and I, following our studies of effects of *spatial* distribution of dose (May75), have been considering the analogous time effects, and I would like to conclude with a very brief summary of some of our thinking.

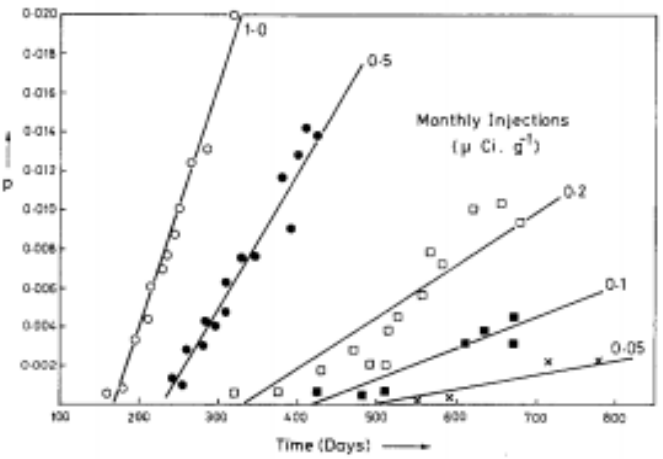

FIG. 2. Probability of an osteosarcoma in mice (per animal per day) (Br49).

We have approached the problem a little differently, abandoning the idea of a single latent period and asking rather: is there experimental evidence as to the form of the variation of probability of tumor appearance with time following an element of exposure? That is: what is the form of a possible probability density function? On integration this form must evidently be such as to yield the familiar linear or S shaped (ogee) response curve against time or perhaps dose.

Having been involved some forty years ago with Kennaway and his team (Co32) in the identification of aromatic hydrocarbons as the first "pure" carcinogens, and having still a feeling that radiation and chemical carcinogenesis must eventually be brought together, I looked first at some of the vast literature of chemical carcinogenesis. In 1967 Druckrey (Dr67) published an impressive account of an extensive series of investigations into quantitative aspects of various chemical carcinogens, in which he established that the numbers and times of appearance of tumors were log-normally distributed against total dose (Fig. 3). For continuous dosage this often implies log-normal distribution of time of appearance. Moreover, if d is the daily dosage and t the median induction time, he also established a relationship (namely, $dt^n =$ constant), with n varying from about two to six, in different experiments with different materials. Results of this form have been obtained by many other workers with a range of chemical carcinogens (Ar68) and in investigations extending even to cancer in smokers.

Since preparing the circulated text of this lecture, I have looked again at some of the results obtained by Kennaway, Cook, Hieger, and myself (Co32) on all the tumors obtained by continued painting of 1:2:5:6-dibenzanthracene on 19 series of mice and 107 tumors (273 animals). The times of appearance are surprisingly accurately distributed as Gaussian normal (Fig. 4) rather than log-normal, but this is a heterogeneous set of animals and conditions, though always the same agent. I am not sure what this proves, except perhaps that I have not rushed into publication, for the results were obtained 45 years ago in 1932 and are the earliest known to me for the effects of a chemically identified carcinogen. Later results with 1:2:5:6-dibenzanthracene have yielded a log-normal distribution.

Other Druckrey results (Fig. 5) indicated a larger value of the standard deviation σ for leukemia than for solid tumors, a point to which we will return later. The shorter latent

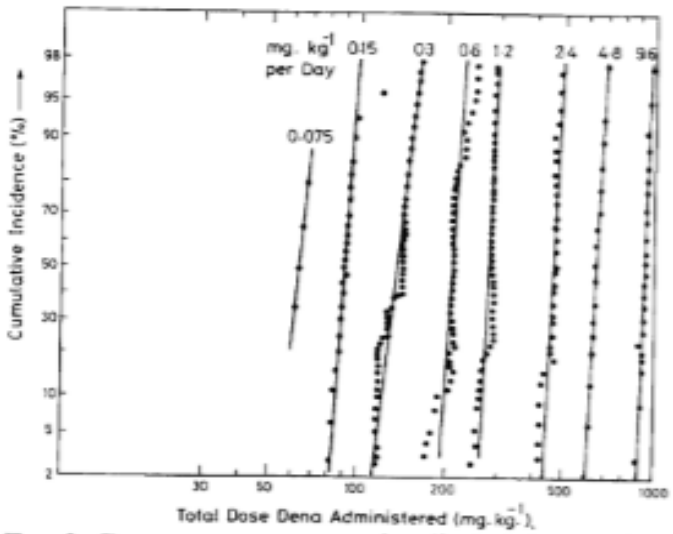

FIG. 3. Dose-response curve for diethylnitrosamine (DENA) in rats (Dr67).

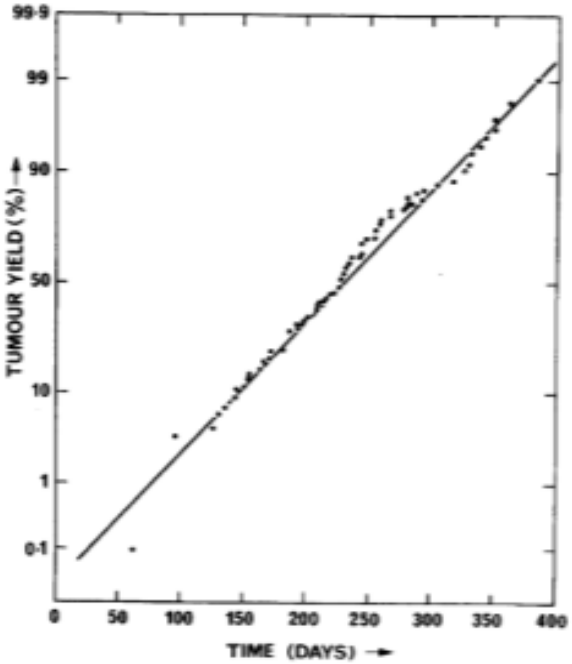

FIG. 4. Times of observation of tumors produced by 1:2:5:6-dibenzanthracene (Co32).

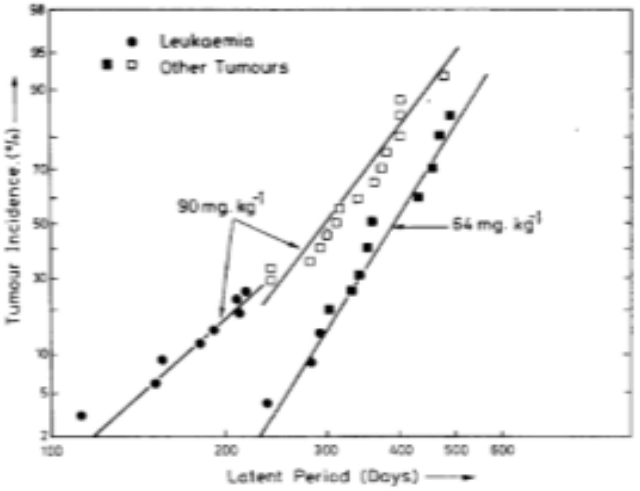

FIG. 5. Carcinogenesis induced by a single dose of methylnitrosourea given intravenously to rats (Dr67).

period at higher dose is also apparent. We see that the tumors are appearing earlier with 90 mg.kg^{-1} than with 64 mg.kg^{-1}. The slope of the curve is, of course, an inverse measure of standard deviation.

We naturally ask: does this same form of dose or time relationship hold for radiation carcinogenesis? Experiments by Blum (B159) with ultraviolet light indicate that it does very precisely, while recently Albert and Altshuler (A173) produced evidence that for ionizing radiations the log-normal form is again at least a useful approximation (Fig. 6), which may be used to calculate, for example, the average life shortening of an irradiated human population. While feeling considerable scepticism about any "universal" relationship in biology, there does seem sufficient evidence to justify a particularly careful look at this log-normal form of time delay.

We must leave aside mathematical detail, but may I just remind you that the log-normal density distribution is indeed Protean (Figs. 7 and 8), being nearly Gaussian for low values of the standard deviation (σ); while for higher values of variance (σ^2), that is, greater heterogeneity of the "population", the density becomes very skew with highest values of probability (mode) at low values of the variable. When we integrate to obtain cumulative response functions against time (and perhaps dose), we deduce responses of

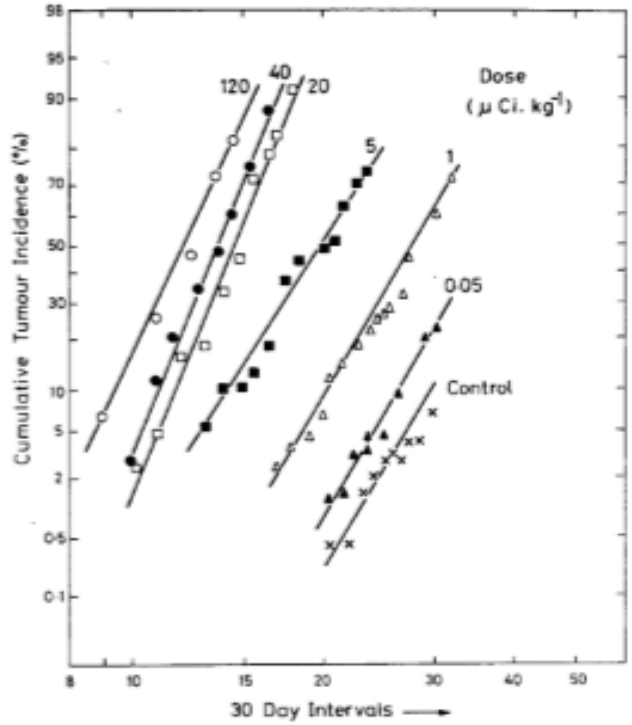

FIG. 6. Cumulative incidence of osteosarcoma in rats following single injection of ^{226}Ra (Al73).

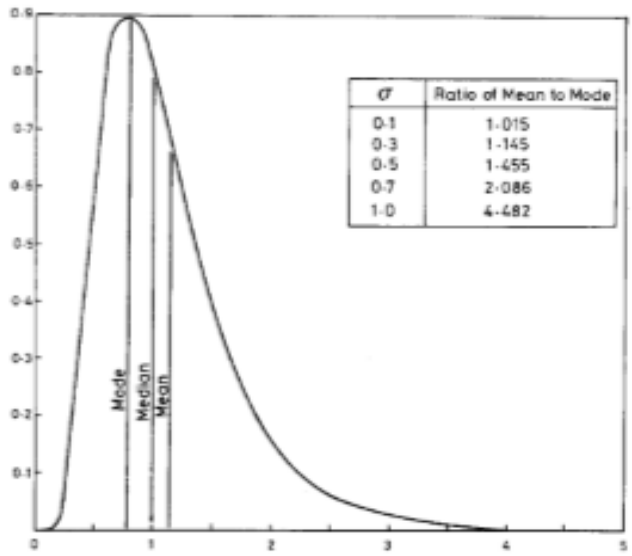

FIG. 7. Features of the log-normal distribution.

varying shapes depending greatly on the variance and median. We have three variables—time, variance, and response—so that we need a surface to represent our data. My colleague, Dr. Clarke, has produced computer generated drawings of such surfaces as, for

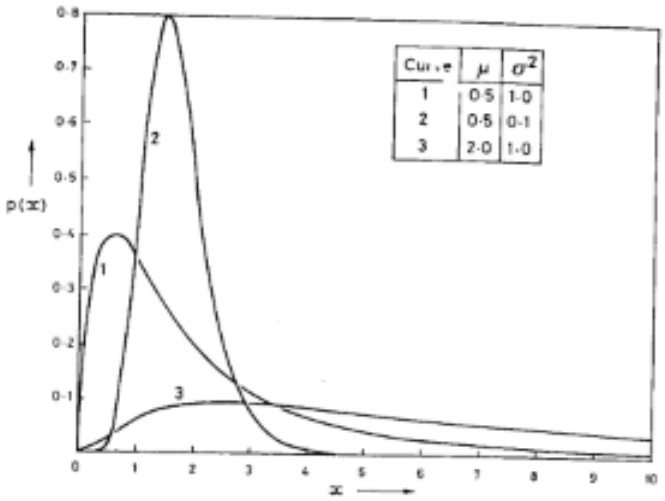

FIG. 8. Examples of the log-normal distribution.

example, that showing probability density (Fig. 9) or integrated response (Fig. 10). When we integrate for small σ we have the "threshold" phenomenon, and for large σ the gradual, almost linear response. For ease of demonstration it is convenient (Fig. 10) to reverse the previous direction of viewing the section of the surface, so that small σ is now at the front and large values of σ behind.

May I add that we have recently analysed as probits a number of sets of data and found approximate agreement with this form. Experimental data expressed as "logit" are probably satisfactorily recast as "probit". We have also investigated changes of σ with dose and with concentration of radioactive

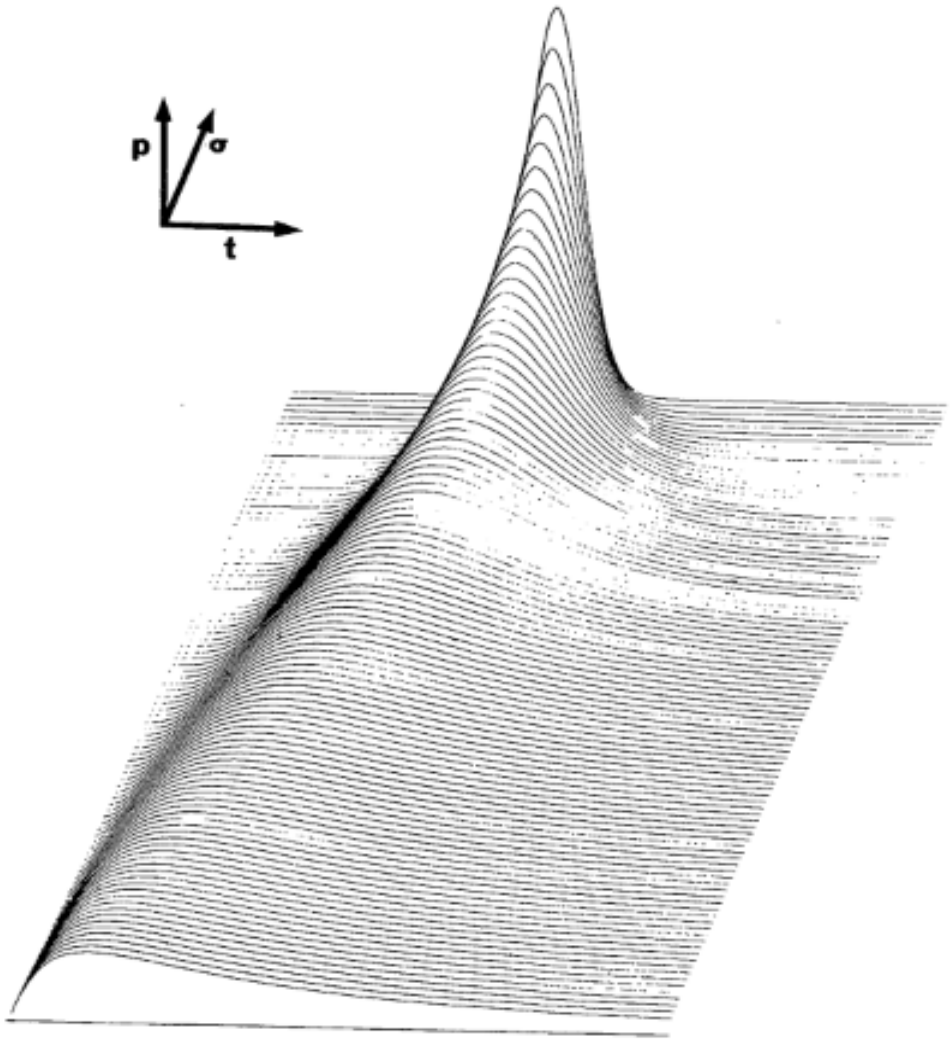

FIG. 9. Log-normal probability density distribution with a constant median at 0.4 of the time scale and σ decreasing linearly from 1.0 (front) to 0.1 (back).

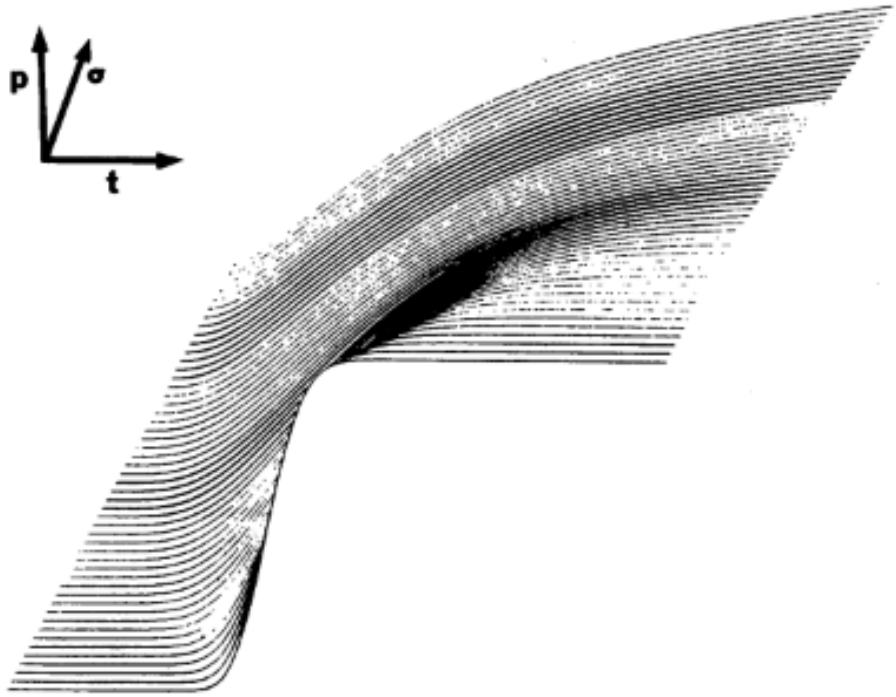

FIG. 10. Integrated log-normal probability density distribution with constant median at 0.4 of the time scale and σ increasing linearly from 0.1 (front) to 1.0 (back).

material as "point sources." Data on leukemia in Hiroshima appear to fit this form (Fig. 11) (Un72a). The crude data are worthy of much closer analysis than we have given them up to the moment. It is interesting to try to study possible variation of σ with dose. Figure 12 is derived from Robley Evans's

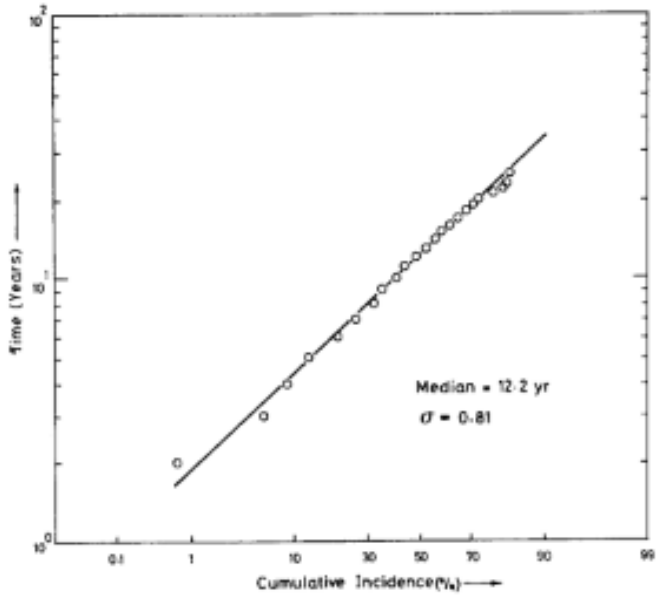

FIG. 11. Incidence of leukemia among Japanese survivors from Hiroshima.

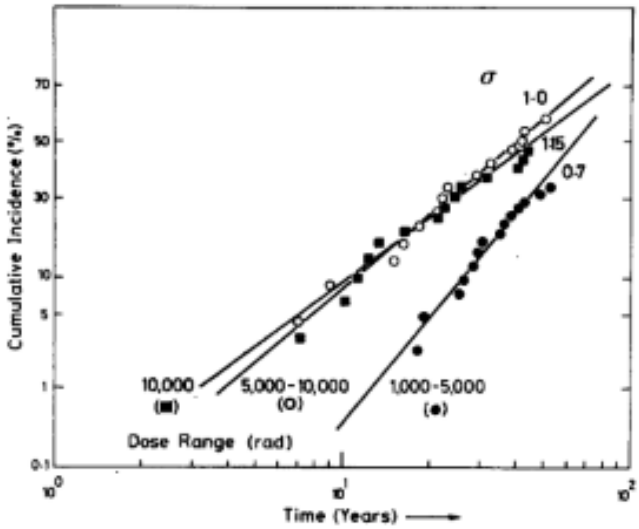

FIG. 12. Tumor appearance time for varying dose ranges.

data on tumor appearance time vs average skeletal cumulative rads for a group of radiogenic tumor cases. Again, much closer analysis is required. Here we merely indicate that similar relationships hold and may be dependent on dose range (Ev74).

What does all this imply? One thing it does *not* imply namely, that there is any exclusive correlation between the log-normal

distribution of time delay and cancer. The form is of extremely general application far outside our field, in biology, economics, physiology, psychiatry, chemistry, and even the study of conservation of works of art, or routine observations of the gamma-ray dose around fuel element treatment ponds at AERE. Size of crushed stones, distribution of incomes, ages at first marriage, number of words in simple sentences by Chesterton, Wells, and Shaw also fit this form! Essentially we have moved from the study of individual interactions to the statistics of heterogeneous populations. Let me quote just one example of how these ideas may help us.

In the 1972 Report of UNSCEAR (Un72b) there is a very interesting paragraph that reads as follows: "The data from experiments with low LET radiation suggest that the more *resistant* the tissue to tumor induction, the more likely that the dose response will be *curvilinear* or *sigmoid*, and the more *sensitive* the tissue to radiation, the more likely that *linear* dose-response curves for tumor induction will be observed. Likewise, linear dose-response curves are seen where the spontaneous incidence of neoplasms is moderate to high, further suggesting that linearity of the dose-response curve is related to sensitivity to tumour induction."

Our integrated response curves show precisely this. "Sensitive tissue" corresponds to low median dose (or time) and large variance since this brings low values of "mode", in which circumstances rough linearity is predicted by our integration. As noted above, interestingly enough, our detailed analysis shows, too, that in both Druckrey's chemical experiments and in Court-Brown and Doll's and Japanese data for leukemia, the standard deviation of the log-normal plot for these diseases is higher than for most solid tumors. Coupled with low median dose, this immediately leads to the prediction of a roughly linear response, raising again the question as to whether the leukemias are not a very complex set of diseases arising from a very heterogeneous set of cells. It is of interest that from a different point of view Baum (Bau73) discussed population heterogeneity in relation to radiation-induced cancer. A study of the log-normal cumulative probability curves shows how easily various linear or power law response curves may be derived following variation of σ. Figure 13 shows the effect of reducing the median time linearly with the increasing dose. If σ is essentially constant at 0.1 (front), a fourth power law is expected. If σ increases linearly with dose, the apparent dose–response relation becomes roughly a square law.

We have recently extended our calculations to more complex situations in which the (median) latent period is assumed to decrease with the dose already delivered, this again producing changes in the expected response curves, in particular predicting high response at long times.

It is clear that the assumption of a probability density function for "latent period" opens new possibilities in interpretation of response functions, particularly for continuous irradiation with low LET rediations. There is some evidence of log-normal survival curves, and Fig. 14 shows theoretical survival curves obtained by integration of log-normal distributions with varying parameters. We note the similarity of our theoretical survival curves with those so well known in radiobiology with their linearity of log survival at high dose, their "shoulder", and extrapolation number, all derived from Poisson statistics. My own belief with respect to carcinogenesis is that the preliminary transformation may well be determined as in Poisson statistics, but superimposed is a probability density function determined by the nature and life histories of the transformed cells. A combination of cell survival and probability of tumor incidence may be used to predict peaked response (Fig. 15).

Let us agree, that radiation confers a distributed probability of a future event, carcinogenesis. How is the probability, as it were, "conveyed" in time, and how is it eventually "realized"? We must, I think, turn to molecular biology. Modern biology has become increasingly interested in the mechanisms of transference of instructions required by a living cell to continue its metabolism, to transmit the required information to the next generation of cells

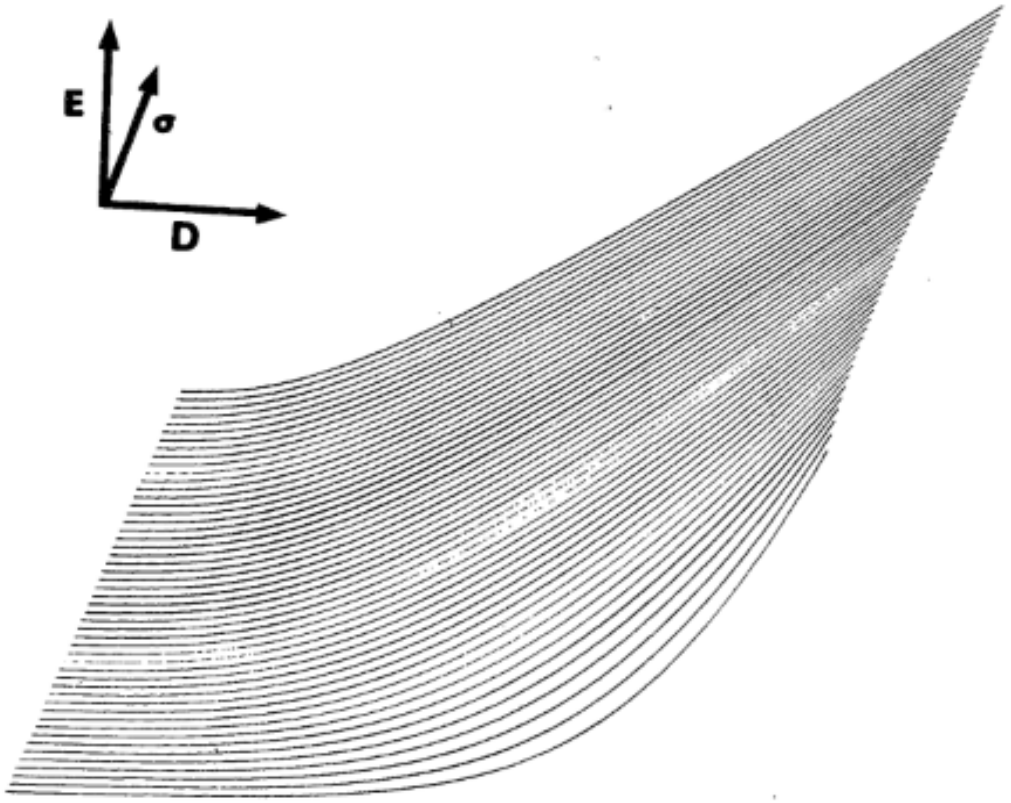

FIG. 13. Cumulative probability curve derived assuming log-normal time of appearance of effect, response directly proportional to dose, and median time reduced linearly with increasing dose by 30% over dose range.

when it divides or perhaps differentiates into a cell destined to perform a specific function in the organism. Radiation causes point mutations, chromosome aberrations, and innumerable transient changes, thus destroying organization, increasing entropy, interfering with information transfer, and increasing confusion (Yo58). Mathematical Information Theory in one form (Fi53) links "information" with the reciprocal of the variance of a "normal" population, just as we have linked the shape of the response curve. A cell lineage is a communications system and it is therefore not surprising that so-called Information Theory or Communication Theory seems to furnish the appropriate mathematical techniques. We move towards our biological colleagues in assuming heterogeneity and try to extract useful information from that diversity. Cell turnover times are sometimes log-normally distributed; "latent period" may be drastically reduced by the application of noncarcinogenic "promoters" or viruses. Cells respect metabolic change rather than the dials of grandfather clocks! Maybe we have now the possibility of improving on the rather disappointing contributions from Information Theory as applied to biology in the 1950's.

I think we must, in any case, move towards human biology. As physicists or engineers we are apt to concentrate excessively on the quantity we can measure—namely, dose. This remark perhaps comes strangely from one like myself after a lifetime of interest in dosimetry, though I have always regarded it as merely a step towards biological understanding, but if we wish to take the important step from measuring dose to assessing risk to individuals and populations, we shall be forced to pay more attention to and to understand more of biological phenomena. It happens that biophysics and biomathematics, with the help of computer technology, are poised for rapid, if somewhat erratic, advance (Ba75). Let us not forget that our aim

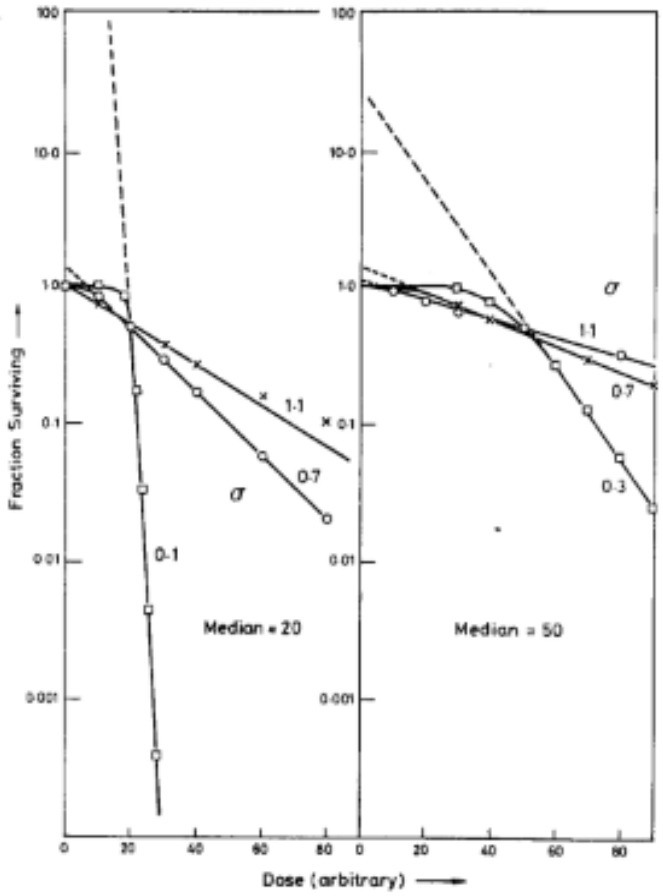

FIG. 14. Survival curves for log-normal distribution of cell killing with dose.

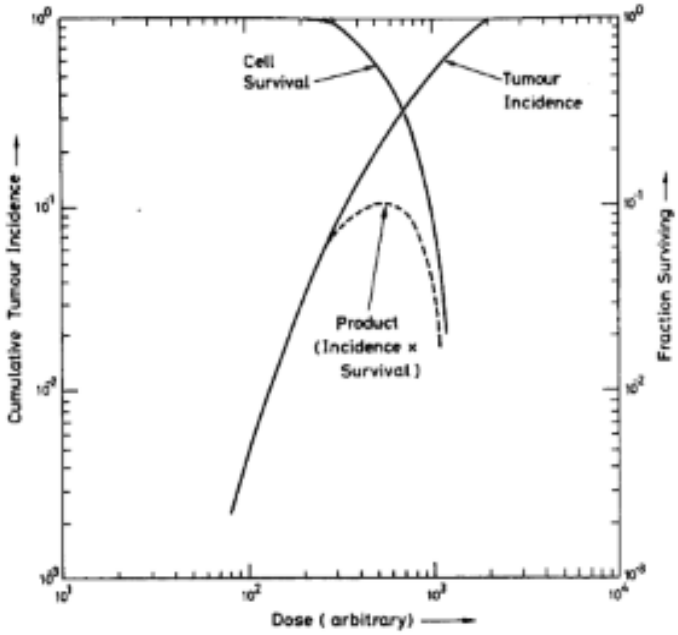

FIG. 15. Hypothetical dose–response curve generated from log-normal distribution of incidence with time and cell survival with dose.

is to protect people, not amass dose or other statistics, though that is a useful and, indeed, indispensible activity.

But, you will say, shall we not as practical men be forced at present to use empirical relationships to make our practical decisions? Yes—we shall; but being old-fashioned I still think that Science has something to do with understanding as well as manipulating phenomena to our own ends.

Such progress as we have made in the protection field has certainly arisen from careful and intensive empirical observation but also from attempts to understand mechanisms as, for example, those of mutagenesis and carcinogenesis. Such understanding has profoundly influenced our decision-making. I have no doubt that the increase in knowledge of biological mechanism now taking place will influence the scientific basis of protection against all environmental hazards, including radiation. In spite of the abuse sometimes leveled at us we have a sounder quantitative basis for our decisions than for those in any other "safety" field. We must, nevertheless, use every endeavor to strengthen our basic knowledge and widen our horizons. I make no apology for directing your attention to these basic concepts and how they may change in the future.

Moreover, since the theme of this Congress is "Radiation protection as an example of action against the hazards of the modern world", I hope you think it appropriate for me to have tried to link together chemical and radiation carcinogenesis in a common biological and mathematical framework, searching for a common quantitative attack on a common risk.

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REFERENCES

Al73 Albert R. E. and Altshuler B., 1973, "Considerations Relating to the Formulation of Limits for Unavoidable Population Exposures to Environmental Carcinogens", in: *Radionuclide Carcinogenesis*, Atomic Energy Commission Symposium Series No. 29, p. 233 (United States: AEC).

Ar68 Arcos J., Argus M. F. and Wolf G., 1968, *Chemical Induction of Cancer* (New York: Academic Press).

Ba75 Bartlett M. S., 1975, *Probability Statistics and Time* (London: Chapman and Hall).

Bau73 Baum J. W., 1973, "Population Heterogeneity Hypothesis on Radiation Induced Cancer", *Health Phys.* **25**, 97.

Bl59 Blum H. F., 1959, *Carcinogenesis by Ultra-Violet Light* (Princeton, NJ: University Press).

Br49 Brues A. M., 1949, "Biological Hazards and Toxicity of Radioactive Isotopes", *J. Clin. Invest.* **28**, 1286.

Co32 Cook J. W., Hieger I., Kennaway E. L. and Mayneord W. V., 1932, "The Production of Cancer by Pure Hydrocarbons", Part 1, *Proc. R. Soc. B*, **111**, 455.

Dr67 Druckrey H., 1967, "Quantitative Aspects in Chemical Carcinogenesis: Evaluation of Risks", in: *Potential Carcinogenic Hazards from Drugs*, Union Internationale Contre le Cancer Monograph Series, 7, p. 60 (Edited by Truhaut R.) (New York: Springer).

Ev74 Evans R. D., 1974, "Radium in Man", *Health Phys.* **27**, 497.

Fi53 Fisher R. A., 1953, "Statistical Information", in: *Information Theory in Biology* (Edited by Quastler H.) (Urbana: University of Illinois Press).

Li76 Lindell B., 1976, "Radiation and Man", *Health Phys.* 31, 265.

Ma71 Marinelli L. D., 1971, "The Stability of Leukemogenic Risk in Human Marrow Irradiated by Alpha Rays", Argonne National Laboratory Report 7860, Part 2, p. 184 (July 1970–1971).

Mar75 Marshall J. H. and Groer P. G., 1975, "Theory of the Induction of Bone Cancer by Radiation: A Preliminary Report. I. A Three-Stage Alpha Particle Model and the Data for Radium in Man", Argonne National Laboratory Report 75–60, Part 2, p. 1 (July 1974–June 1975).

May75 Mayneord W. V. and Clarke R. H., 1975, "Carcinogenesis and Radiation Risk: A Biomathematical Reconnaissance", *Br. J. Radiol.* Supplement 12.

Re27 Regaud C. and Lacassagne A., 1927, "Effets histophysiologiques des rayons de röntgen et de Becquerel–Curie sur les tissues adultes normaux des animaux supérieurs", in: *Radiophysiologie et Radiothérapie*, Archives de L'Institut du Radium et de la Fondation Curie, Vol. 1, Fasicule 1. Les Presses Universitaires de France.

Si21 Sievert R., 1921, "Die Intensitätsverteilung der primären γ-Strahlung in der Nähe medizinischer Radium-präparate", *Acta Radiol.* **1**, 89.

Si23 Sievert R., 1923, "Secondary Rays in Radium Therapeutics", *Acta Radiol.* **2**, 268.

Si25 Sievert R., 1925, "Einige Untersuchungen über Vorrichtungen zum Schutz gegen Röntgenstrahlen", *Acta Radiol.* **4**, 61.

Si32 Sievert R., 1932, "Eine methode zur messung von röntgen-, radium- und ultrastrahlung nebst einige untersuchungen über die anwendbarkeit derselben in der physik und der medizin", *Acta Radiol.* Supplement 14.

Si41 Sievert R., 1941, "Zur theoretisch-mathematischen Behandlung des Problems der Biologischen Strahlenwirkung", *Acta Radiol.* **22**, 237.

Un72a Report of the United Nations Scientific Committe on the Effects of Atomic Radiation, 1972. Ionising Radiation: Levels and Effects,Vol. 2 "Effects" Annex H "Radiation Carcinogenesis in Man", p. 408.

Un72b Report of the United Nations Scientific Committee on the Effects of Atomic Radiation, 1972. Ionising Radiation: Levels and Effects, Vol 2. "Effects", paragraph 36, p. 386.

Yo58 Yockey H. P., Platzman R. L. and Quastler H., Editors, 1958, *Symposium on Information Theory in Biology*(Oxford: Pergamon Press).