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This Technical Report represents the text of a lecture invited by The Institute of Management Sciences (TIMS). In non-technical terms it explains certain pitfalls involved in real life public health studies concerned with exposures to low-level irradiation. Two particular recently-announced studies are discussed. The first of them is the study of health effects, particularly cancer, connected with radiation from uranium mill tailings. It is connected with the enactment in November 1978 of Public Law 95-604. The second study was announced last May. It is connected with the accident at the Three Mile Island A-plant.

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20. (Cont. from reverse) While both studies are irradiation oriented, the validity of their conclusions requires taking into account the exposure to noxious chemical pollutants.

PROBABILITY MODELS IN MEDICINE AND BIOLOGY:

Avenues for Their Validation for Humans in Real Life

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1. Introduction. It is a great pleasure for me to respond affirmatively to the invitation of the Institute of Management Sciences (TIMS) to prepare this special invited lecture. There is a great variety of probability models inspired by problems of medicine and biology. In preparing this lecture I select those models that relate to contemporary societal problems, which I expect to be of special interest to TIMS. Their general nature can be symbolized by the term Energy Crisis, Pollution and Health [1].

The two lines of the title of the present paper, the first relating to probability models, and the second to their validation to humans in real life, correspond to the contents of the present article. The source of probability models relating to health, etc., are experiments with animals such as mice, rats, dogs, etc. Here we have to face the necessity to validate the model of the phenomena observed in these experiments. As time goes on and the

experimental work progresses, it frequently becomes clear that this or that constructed probabilistic model is not realistic and must be modified or discarded. Here, considerations of intelligibility (why should one assume any such thing?) dictate a somewhat historical mode of presentation. Also, the presentation is non-technical: no formulas!

All the above relates to probabilistic models, hopefully valid to represent the happenings to lower animals studied in laboratory experiments, customarily conducted with substantial efforts to maintain uniformity of conditions of all the experimental animals, those subject to some "treatment" and also the controls. In fact, inbred animals are frequently used. The situation in real life is very different, especially when humans are concerned. There are genetic as well as socio-economic differences from one individual to the next and also a great variability in environmental conditions. A case in point is the announcement (New York Times, May 30, 1979):

H.E.W. to Study Accident Effects in A-Plant Area.

The area in question is that around the Three Mile Island nuclear plant. The subject of study will be the public health effects of the radiation exposure during the now well-known accident. It is here that the attainment of valid conclusions requires special care. Avenues towards such validity and a variety of pitfalls are described at the end of the present paper.

As mentioned at the outset, there is now a great variety of probabilistic models inspired by problems of biology and health. This creates a difficulty in preparing a not too long list of references. The device adopted is as follows. When an important contribution is due to an individual, say X, the name X is mentioned in the text and is followed by a reference to one of my own papers in which a complete reference to the work of X is given.

2. THE THRESHOLD, my first exposure to a controversial public health problem. During the winter of 1958 I spent some time at the National Institute of Health with the assignment to study the pro-and-con of the "hypothesis of the threshold." As I remember it, this assignment was connected with the appearance of two interconnected papers published in Science. One paper, "Mice, men and fallout," authored by M.R. Finkel [2], summarizes the results of a prolonged empirical study of carcinogenic effects of irradiation. Also, it attempts to estimate the "threshold." The second paper, "Critique of linear theory of carcinogenesis" is due to A.M. Brues [3]. The principal point of this critique is that the "linear hypothesis" implies non-existence of the threshold of exposure to irradiation, below which the irradiation could do no harm.

As mentioned, the controversy about the existence of a threshold was rife in the 1950's. Interestingly, it continues to be

with us now, even though in a different form. Rather than speak of the threshold, some authors use other terms, such as "virtually safe dose" of irradiation, etc. See Science Vol. 198 (1977) pp. 693-697. A contrary view, to which I fully subscribe, is published in Science of May 25, 1979. The headline, p. 811, reads: "How to Assess Cancer Risks."

Briefly and roughly, the arguments of Dr. Brues favoring the existence of a threshold are that the mechanism of carcinogenesis involves at least two stages. First, the living cells of an animal undergo a mutation-like change that may lead to benign (non-cancerous) growth. Cancer begins to develop as a result of another mutation-like change in a cell of the benign growth, a change caused by some carcinogenic agent, perhaps by irradiation.

3. <u>My involvement inspired by Dr. Brues</u>. The probabilistic modeling problem raised by Dr. Brues reduces to the question whether his two step mechanism of carcinogenesis implies the existence of irradiation threshold. In order to answer this question, it was necessary for me to construct an appropriate probabilistic model and to examine its implications. Here, I had a little difficulty due to a degree of vagueness in Brues' arguments. They are exemplified by the following quotation.

> There are many examples of induction of malignant diseases through mechanisms that are clearly indirect -- that is, where the irradiation of a cell can be shown not to be a critical factor....There is a large body of evidence indicating that the malignant transformation occurs after a sequence of "precancerous" stages has taken place. The most widely observed example is in the development of skin cancer,

which, in whatever way it was produced, is likely to be pre-
ceded by various types of benign atrophic or hyperplastic
states; in experimental studies it most often develops in a
benign papilloma.

In order to produce the corresponding probabilistic model, it
was necessary for me to make specific mathematical assumptions about
the multiplication of cells of "benign" growths, etc. My efforts in
this direction made during the stay at the NIH in 1958 were formu-
lated in a mimeographed monograph that was sent around to
individuals expected to be interested. The answer to the question
as to whether the two step mechanism of carcinogenesis implies the
existence of a threshold was found to be negative. Of the several
comments I received, the most consequential was one from Dr. Michael
B. Shimkin. It was to the effect, more or less: "Forget the
threshold. The important question is whether the mechanism
of carcinogenesis is one-stage or multistage."

4. <u>Mechanism of carcinogenesis: one-stage or multistage?</u>
The comment of Shimkin just quoted raised the problem of designing
an experiment that could answer the question in the title of the
present section. Conversations with Shimkin, then at Tempel Univer-
sity in Philadelphia, resulted in a several year long three-way coor-
dinated study, with Shimkin in the East, M. White, A. Grendon and
H.B. Jones at the Donner Laboratory in Berkeley and with E.L. Scott
and myself in the middle [4]. Among other things, this involved
a detailed review of a substantial probabilistic-statistical liter-
ature on the subject. From the point of view of probabilistic

modeling contributions of the following authors must be mentioned: (i) N. Arley and S. Iverson, (ii) P. Armitage and R. Doll, (iii) T.E. Harris, (iv) D.G. Kandall and (v) W. Klonecki.

Very extensive and outstanding experimental work on the mechanism of carcinogenesis has been done by Shimkin and Polissar [4]. However, contrary to the interests of Brues, they were concerned with chemical carcinogenesis. Specifically, Shimkin and Polissar were working on lung tumors in mice that received injections of a chemical, namely urethane: Table I, reproduced from [4], summarizes their findings.

It is seen that, for a succession of days after the injection of urethane, the consecutive columns of the table give mean numbers of presumed first mutant cells, of the so-called "hyperplastic foci" per lung of the mice, and of tumors per lung. The lower part of the same Table I gives a graph characterizing the change in the number of tumors per lung with the increase of time since the injection: rapid growth during first 50 days and then stabilization.

The summary of the findings is somewhat as follows. As time goes on, the number of supposed mutant cells and also the number of the hyperplastic foci begin by increasing and then go down. The number of foci per lung reaches its maximum at 4 to 5 weeks after urethane. At about the same time tumors begin to be counted. The first average given is 15.5, the last is 35.7.

TABLE I

COUNTS OF CELLS, OF HYPERPLASTIC FOCI, AND OF TUMORS IN LUNGS OF MICE
After Shimkin and Polissar [12].

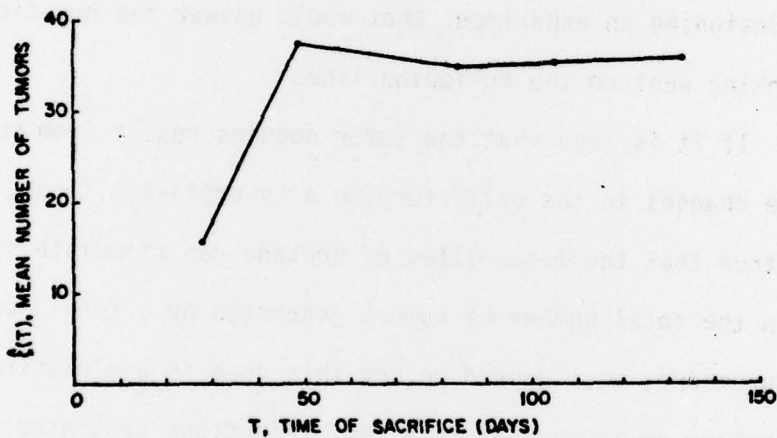| Days after Urethane	Cells per Square	Presumed First Mutants per Square (106.3 sq. micra)	Foci per Lung	Tumors per Lung
0	0.73	0.00	—	—
1	0.85	0.12	—	—
3	0.92	0.19	—	—
7	1.11	0.38	—	—
14	1.02	0.29	294	—
21	1.35	0.62	450	—
28	1.57	0.84	390	15.5
38	—	—	610	—
49	1.33	0.60	450	37.3
84	1.20	0.47	260	34.8
105	—	—	200	35.2
133	—	—	83	35.7

FIGURE 2

Estimated mean number of tumor nodules per lung.
Each mouse received same dose of urethane 1 mg/gm BW,
sacrificed at varying times *T* after injection.
Data from Shimkin and Polissar [7].

If my memory of conversations with Shimkin does not fail me, the smallest tumor noticed and counted was composed of 34 cells.

With these empirical data, the question about one-stage or multistage/mechanism of carcinogenesis reduces to the following: are the hyperplastic foci and the tumors independent parallel developments following the injection of urethane, or, alternatively, do the tumors result from a mutation-like change occurring in the hyperplastic cells? In this latter case, the hyperplastic cells would be some kind of predecessors of tumors. The experimental data available at the time were not sufficient to answer this question, and our Stat. Lab. group felt fascinated by the possibility of designing an experiment that would answer the question. Our thinking went on the following lines.

If it is true that the tumor nodules result from mutation-like changes in the cells forming a hyperplastic focus, and if it is true that the metabolites of uretane can stimulate such mutations, then the total number of tumors generated by a total dose, say D, of urethane, must depend on how this dose is administered: in one injection or in several, say two, injections separated by a suitable interval of time. If the second injection occurs at the time when the hyperplastic foci contain many cells, the number of tumors counted at a substantially distant time would be larger than in the case when the number of such cells is small. On the other hand, if the mechanism of carcinogenesis is one-stage, the total number

of tumors counted would be independent of whether the total dose
D of urethane is administered in a single injection or in several
fractions.

As mentioned, considerations of this kind proved inspiring
and resulted in a number of experiments on both sides of
the continent. Each experiment used a fixed dose D of urethane
administered in a single injection and also in several equal
fractions separated by a varying number of days. The response
variable was the number of tumors counted. One of the complications
involved was the difficulty of noticing a tumor when it is very
small, like the one mentioned above, composed of only 34 cells.
The mathematical treatment included the consideration of prob-
ability that a tumor composed of some n cells will be counted.
The contributors to this problem included D.G. Kendall [4].

The final result of these experiments favored the multi-
stage mechanism of carcinogenesis [4].

5. A probabilistic model stemming from medicine. The models
considered thus far were generated by problems of biology: what
is the mechanism of carcinogenesis? The purpose of this section
is to illustrate a relatively easy probabilistic modeling by
L.M. Le Cam related to a very interesting problem of immunotherapy
of cancer conducted by Vera S. Byers, an immunologist, and Alan
S. Levin, an M.D. [5].

Cancer cells removed from a patient can be kept alive in a

laboratory. In appropriate conditions they can multiply. Colonies of such cells are being used for experiments (in vitro) intended to discover agents that can kill them. One such agent is pure distilled water. Live cancer cells, irrespective of the kind of cancer, immersed in distilled water are killed within a relatively short time. For this reason, the effectiveness of other cancer-killing agents is determined by comparing it with that of distilled water. This comparison is the basis of the so-called "efficiency index."

The cancer-killers studied are biological entities called lymphocytes present in our blood. As found by Byers [5], the lymphocytes of different individuals vary considerably in their cancer-killing ability. Another important finding is that the cancer-killing ability of the lymphocytes is cancer-specific. The lymphocytes that are efficient in killing cancer of the breast may be very inefficient in killing cells of other cancers. This fact brought out the question about the origin of this cancer/type specificity of the lymphocytes. Can prolonged personal contacts with cancer patients have anything to do with it?

Figure 1, reproduced from [5] provides the answer to this question.

The figure shows two empirical distribution functions of the efficiency index of the lymphocytes. The one on the left corresponds to people who had no known contacts with patients
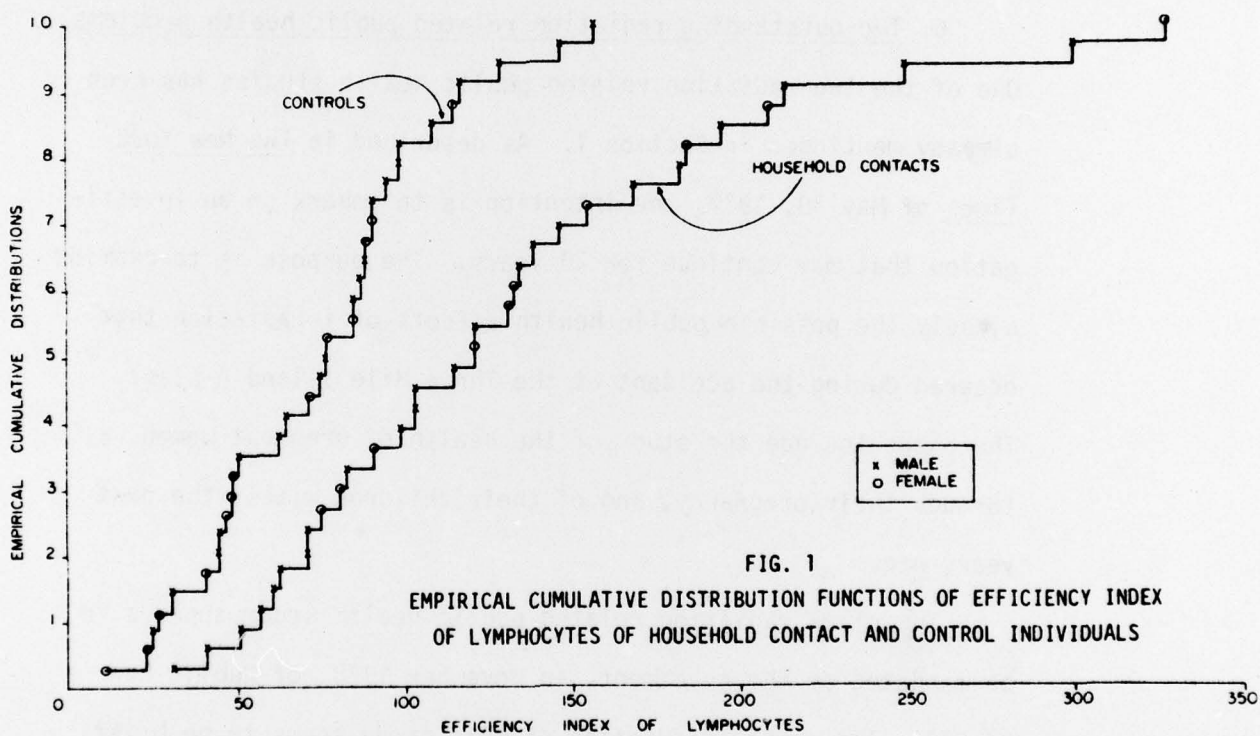
FIG. 1

EMPIRICAL CUMULATIVE DISTRIBUTION FUNCTIONS OF EFFICIENCY INDEX
OF LYMPHOCYTES OF HOUSEHOLD CONTACT AND CONTROL INDIVIDUALS

suffering from cancer of the breast. The other distribution function corresponds to individuals, termed "household contacts," who had prolonged personal contacts with such patients. The two distributions are so widely different that there is little doubt that the lymphocytes of persons having contacts with the cancer of the breast patients are generally much more efficient in killing breast cancer cells than those of the controls.

I consider the above findings most interesting and wish the three scholars all good luck in their further studies.

6. Two outstanding radiation related public health problems. One of the two radiation related public health studies has been already mentioned in Section 1. As described in The New York Times of May 30, 1979, the intention is to embark on an investigation that may continue for 20 years. The purpose is to examine closely the possible public health effects of irradiation that occured during the accident at the Three Mile Island A-plant. The plans include the study of the health of pregnant women, all through their pregnancy, and of their children within the next year, etc.

The other radiation related public health study appears to be mandated by the enactment, in November 1978, of Public Law 95-604. The proposed duration of this study seems to be brief, but its geographical scale is impressive. So are the circumstances: a public upheaval. According to The Washington Post of July 26,

1978, this is what happened:

> Utah Gov. Scott M. Matheson told a Senate
> panel yesterday that the federal government
> is responsible for a serious cancer threat
> in his state from radioactive uranium mill
> wastes and it should pay the whole cost of
> their removal.
>
> About a half-million persons live near a
> 107-acre uranium mill "tailings" pile that
> makes downtown Salt Lake City "one of the
> largest microware ovens in the West."
> Matheson testified at the Senate Energy
> subcommittee hearing....Berrick also sug-
> gested the estimated 23 million tons of
> tailings at abandoned mines are only a
> "bucket in the bathtub" of the larger problem...

The contemplated "removal" of tailings does appear costly.
The proposal is to move by rail not only the pile of tailings,
but also two feet of earth beneath it, to a remote desert site,
90 miles west of Salt Lake City. The incident initiated by the
governor of Utah attracted the attention of officials in quite
a few localities marked by the presence of the uranium mill
tailings all over the country. As a result, the contemplated
public health study is likely to cover a very large geographical
area.

The help of TIMS to reach valid conclusions in both radiation
related public health studies may be very important.

7. <u>Some anticipated difficulties</u>. Possibly, the principal
difficulty of the two radiation related public health studies
is psychological in character.

As discussed in the earlier section of this article, there

is now no room for doubt that exposure to irradiation does involve health hazards, particulary the danger of cancer. Thus, THERE IS THE POSSIBILITY THAT THE INVESTIGATORS CONCERNED WILL FOCUS THEIR EFFORTS ON RELATING CANCER AND OTHER HEALTH TROUBLES TO IRRADIATION ALONE. However, as illustrated in Section 4 relating to urethane and its metabolites, there is now little room for doubt that cancer can be also initiated by chemicals, whether in a one-stage or a multistage mechanism. Also, referring to the opinion of Brues, there may be the phenomenon of synergism: in order for irradiation to trigger cancer, some "precancerous" benign changes in the relevent cells must take place.

It follows that the concentration on the relationship between cancer and environmental radiation would be a dangerous policy. Obviously, if an important chemical pollutant is left out of the investigation, then this pollutant's carcinogenic effects will be attributed to irradiation, but very likely in a messed-up manner. A possibility of this happening will be documented in the next section. At the moment I wish to emphasize that, in order to achieve validity, the two contemplated epidemiological studies must be MULTIPOLLUTANT and MULTILOCALITY studies. Otherwise, the conclusions reached may be misleading. The multilocality element is needed as "an avenue to validation for humans in real life" of the validated experimental findings on carcinogenesis.

8. What can happen if an important carcinogenic pollutant
is excluded from a real life cancer oriented study? An illus-
tration of the possible unpleasant consequences is provided by
an impressive multilocality study [6] prepared by four authors,
all affiliated with the University of Pennsylvania, Philadelphia:

> R. J. Hickey and E. B. Harner, Institute for Environ-
> mental Studies

> D. E. Boyce, Regional Science Department, Wharton
> School of Finance and Commerce

> R. C. Clelland, Department of Statistics and Operations
> Research, Wharton School of Finance and Commerce

While the above affiliations indicate competence, they also
show a reasonable "practical" slant likely to be appreciated by
TIMS. The Abstract of the paper states in part:

> Ecological statistical studies employing methods
> of multivariate analysis, based on a radiomimetic
> or mutagenic hypothesis, have yielded a number of
> statistically significant multiple regression equa-
> tions in which concentrations of environmental
> chemicals, largely air pollutants, predict annual
> mortality rates for major categories of cancer and
> heart disease, as well as for congenital malforma-
> tions, for populations of 38 metropolitan areas
> of the United States....

> Among the chemical predictors whose atmospheric
> concentrations are frequently found positively
> correlated with mortality rates are SO_2, NO_2,
> and particulate sulfate. Among frequently recurring
> negatively correlated predictors are Cu, Cd, and Ti.
> Evidence regarding whether SO_2 and NO_2 may be con-
> sidered as mutagenic hazards to life is discussed,
> as are some potentially relevant biochemical func-
> tions of the metals.

The reader's attention is called to the analogy of the four
authors' aims, particularly with respect to cancer and congenital

diseases, on the one hand, and the interests of the just announced Three Mile Island A-plant study. The difference, a striking difference, relates to the agents studied; several chemical pollutants, on the one hand, and irradiation, on the other.

Another fact deserves attention. This is that the four authors' study speaks of "predictors...correlated with mortality rates" that are the focus of their interest. Here one might suspect a reference to a causal relationship. However, as stated in the body of the paper, "Statistical correlations alone, of course, do not and cannot establish causality." Other passages of the paper mention "low levels of ionizing radiation, which is mutagenic." However, no attempt was made to include radiation among the "predictors" studied. The reasons are unclear.

Now, about the findings. As mentioned in the Abstract, the four authors find the mortality rates of the population to be POSITIVELY correlated with the proliferation of SO_2, NO_2 and particulate sulfate. On the other hand, the mortality rates were found to be NEGATIVELY correlated with the Cu (copper), Cd and Ti. The details, given in the main body of the paper, specify that air pollution with copper is NEGATIVELY correlated with mortality from breast cancer and with mortality rates from lung cancer. The negative regression coefficients in these cases are -1.510 and -2.197, respectively, both significant at 1%.

Certain biologists and medical men, with whom these findings

were discussed, find them unexpected. One may hope that the
two announced cancer/radiation studies will not exclude chemical
pollutants as possible noteworthy "predictors." Here, an in-
formed influence of TIMS could be helpful.

ACKNOWLEDGEMENTS

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