STOCHASTIC MODELS FOR CARCINOGENESIS

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1. Introduction

In the last ten years or so a number of papers have appeared, putting forward models of varying degrees of mathematical complexity to describe some of the processes underlying the phenomenon of carcinogenesis. None of these models has gained general acceptance; nor has any clear body of evidence been marshalled which would exclude any of these models from further consideration. One should perhaps consider whether further development of models of this type is profitable at the present time. There is, of course, a danger that models which provide a reasonable description of certain observations may be entirely misconceived. For example, the rapid rise with age in rates of mortality from certain types of cancer, with which some of the models are particularly concerned, is simulated by the pattern of mortality from some other causes, such as accidents, for which the models are clearly inapplicable. There are, we think, two main reasons for maintaining a cautious interest in this topic. One is that many of the concepts on which the models were based were put forward originally by workers in the cancer research field before being formulated in mathematical terms. Salaman [1] points out, for example, that the concept of a number of qualitatively different stages in carcinogenesis was discussed by various workers, including P. Rous and I. Berenblum, between 1935 and 1947. Consequently, there are fairly well established experimental grounds for the formulation of some of the models, and it is reasonable to inquire whether these models satisfy the quantitative, as well as the qualitative, aspects of the data. Secondly, in the present state of ignorance of the biological mechanism of carcinogenesis, it is possible that the mathematical concepts which are evoked to satisfy the available quantitative data might suggest possible lines for future experimentation.

One purpose of the present review is to attempt a unified approach to the various models which have appeared in the literature. This is of some value in indicating that certain features follow as consequences of a general model which embraces many of the particular models. Secondly, we have tried to show the extent to which the different models provide satisfactory descriptions of observed phenomena. The difficulties in covering the literature of relevant experimental data are formidable, and we have not attempted here a general review (which

is, however, much needed). The nature of the available data is described briefly in section 2. We do not put forward any new models, nor do we suggest that there is overwhelming evidence in favor of any one viewpoint.

Any general survey of this field is handicapped by the lack of a widely accepted system of nomenclature, particularly for the various time intervals involved. We have tried throughout to use the system shown in figure 1.

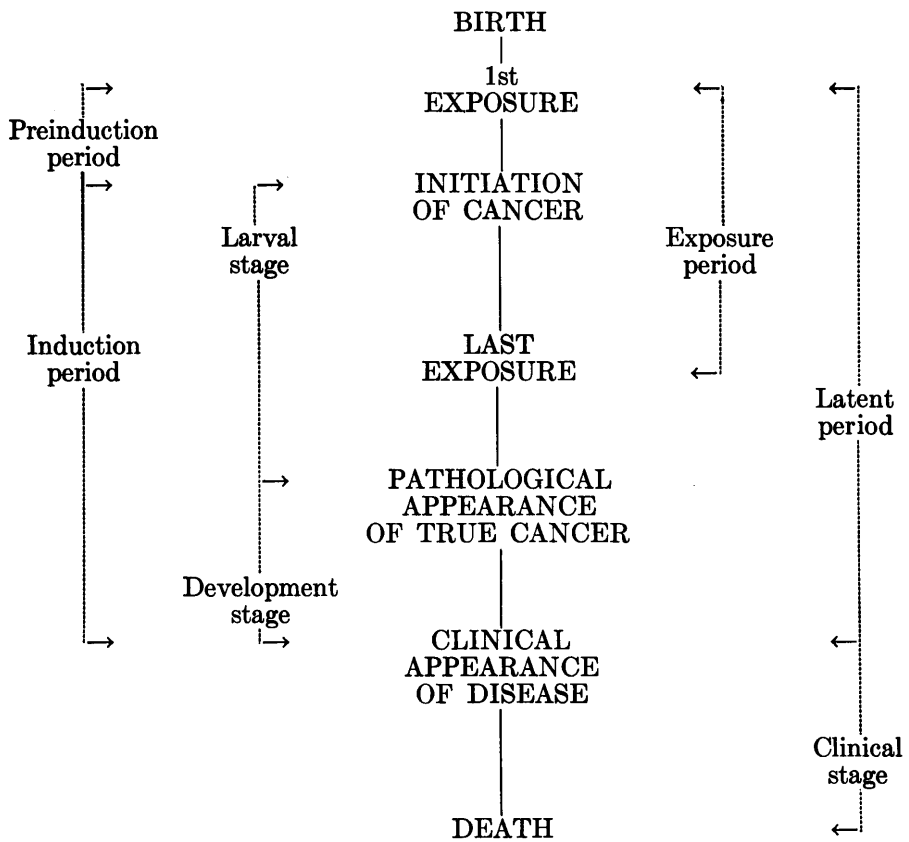

FIGURE 1

On the right in the figure are defined the observable time intervals, and on the left are those of primarily theoretical interest. In certain circumstances, some of the points of time will coincide. If one is considering exposure to the normal environment, the instant of first exposure will coincide with birth (or may precede it). For exposure to a single dose of irradiation, the *exposure period* will virtually disappear, and the *latent period* will coincide with the *induction period.* In models which require only one step from the normal cell to the truly malignant, there will be no *larval stage* and the *development stage* will coincide with the *induction period.*

2. Observational data

2.1. *General.* Experiments in the production of cancer have, for obvious reasons, usually been carried out on small mammals. There are, however, difficulties about the use of such experimental data for testing models of carcinogenesis. First, the numbers of animals employed are usually too small for a reliable estimate to be made of the quantitative relations between dose of carcinogen, duration of exposure, latent period and incidence; in particular, there is little or no available information about these relationships for low levels of incidence. Secondly, it does not necessarily follow that mechanisms which result in a high incidence of cancer among pure bred lines of a susceptible stock are of general application.

Human data have the advantage of being available for such large populations that variations in incidence due to random fluctuation can often be ignored. They have the disadvantage that it is seldom possible to obtain numerical details of the dose of carcinogen or of the date of its application. Nevertheless, one of the primary objects of studying the mechanism of carcinogenesis is to discover how cancer is induced in man and it seems reasonable to examine any proposed model in the light of what little information about human cancer is available.

2.2. *Human data.*

2.2.1. *Details of exposure known.* The only type of human cancer for which exact details are known of the time relation between the application of the carcinogen and the clinical appearance of the disease is cancer induced by a single exposure to a large dose of external irradiation. The time relations between the clinical onset of acute leukemia and of chronic myeloid leukemia and exposure to irradiation in Hiroshima as a result of the atomic bomb expolosion have recently been analyzed by Heysell et al. [2]. The incidence of leukemia began to rise within a few years of the explosion, reached a peak after five to eight years and subsequently declined; after 12 years the incidence had, however, still not reached the base line from which it is presumed to have started. Similar observations have been made by Court Brown and Doll [3] on patients irradiated for ankylosing spondylitis. In their data, however, the peak incidence of leukemia occurred as soon as three to five years after exposure. Morbidity rates observed in Hiroshima are shown in table I. The rates have been calculated from the data published by Heysell et al. [2] and refer only to persons irradiated under 1500 meters from the hypocenter, who have been followed individually. They have been standardized to give the same population of man-years at risk of persons irradiated under 1000 m. for each year of observation (that is, ten per cent) and a constant figure of 0.3 per 10,000 has been subtracted to allow for the cases due to other causes.

For cancer of the thyroid in children following irradiation of the thymus shortly after birth, the induction period has been of the order of five to ten years; but for most other types of radiation induced cancer (for example, cancer of the pharynx or larynx following irradiation of the thyroid for thyrotoxicosis) the

TABLE I

INCIDENCE OF RADIATION INDUCED LEUKEMIA AT HIROSHIMA

Time after Date of Exposure (Years)	Morbidity Rate per 10,000 Persons per Year	Number of Cases
$4\frac{5}{12}$–	4.6	4
$5\frac{5}{12}$–	5.8	5
$6\frac{5}{12}$–	8.3	7
$7\frac{5}{12}$–	3.5	3
$8\frac{5}{12}$–		3
$9\frac{5}{12}$–	2.9	2
$10\frac{5}{12}$–		1
$11\frac{5}{12}$–$12\frac{4}{12}$		4

induction period has usually been over 20 years. No quantitative data are, however, available to enable the distribution of induction times to be analyzed apart from those already referred to for leukemia.

2.2.2. *Age-specific mortality rates.* The most important human data are, perhaps, the age-specific mortality rates which are available in great quantity for many sites in various countries. For most of the principal types of cancer these can be regarded as a good indication of incidence, since the fatality rate is usually high or, if not, is independent of age. British data for many different types of cancer have been examined in detail elsewhere [4]. For most of the principal epithelial cancers, the mortality rises sharply with age from a figure which is close to zero in childhood and adolescence and continues to increase up to 80 years. For some cancers, particularly cancers of the female sex organs, the mortality increases in the usual way up to the age of 50 or 60 years and then flattens out. For others (for example, myelomatosis, cancer of the thyroid and cancer of the salivary gland) mortality increases with age, but the rate of increase is less steep.

A few cancers show double peaks, either in childhood or in adolescence, and in old age. In these it seems most likely that two or more pathological entities have been combined under one rubric. Obvious examples are cancer of the eye (including retinoblastoma and melanoma) and cancer of the kidney (including nephroblastoma and carcinoma). In the case of cancer of the bones, there is a true peak in adolescence, but the second peak in old age is largely an artifact due to the misclassification of cancers which arise primarily in other tissues. The double—or, as it now appears, triple—peak in leukemia mortality is in all probability the result of compounding several separate and independent entities. For chronic lymphatic leukemia the mortality rate increases with age similarly to the principal epithelial cancers; for chronic myeloid leukemia the rate increases steadily but less rapidly; the double peak at ages three to four years and in old age persists in acute leukemia, but it seems possible that with more refined diag-

nosis the peak in early childhood will be shown to be limited to one cytological type.

In the present state of knowledge it seems reasonable to assume that those types of cancer which show an early peak in mortality can be attributed, like the leukemia in Hiroshima, to a single stimulus applied for a relatively short period. In contrast, the cancers which increase in frequency throughout life may, perhaps, be regarded as due to exposure to a carcinogen which is present continuously. It is, therefore, of some interest to examine any proposed model to see whether it can account for these two sets of conditions.

There are, of course, many difficulties in doing this. (i) The mortality rates for many sites vary with time, with the implication that the dose of carcinogen has also varied. (ii) The reliability of the diagnosis on death certificates is questionable and probably also varies with time. (iii) The reliability of diagnosis varies with age; in most instances the recorded death rates are likely to underestimate the true mortality at the highest ages. (iv) The biological situation is different in childhood, when the cell population is increasing, and in adult life. (v) Models are generally concerned with the age at which cancer appears; mortality data are concerned with death. It is possible to make a reasonable estimate of the average duration of the clinical stage of the disease, but the length of the development stage is uncertain.

No set of mortality rates is ideal; among the most suitable are those for cancer of the stomach among men in England and Wales. The changes in mortality have been small and both Stocks [5] and Doll and Armitage [4] have concluded that the cohort born around 1876 is likely to have been exposed to a fairly constant carcinogenic stimulus. The age-specific mortality rates from cancer of the stomach experienced by this cohort are shown in table II. The last age group for

TABLE II

AGE-SPECIFIC DEATH RATES FOR CANCER OF THE STOMACH AMONG MEN IN ENGLAND AND WALES

Age (Years)	Death Rate per 1,000,000 Men
10–	0.24
15–	0.93
20–	3.39
25–	11.6
30–	32.7
35–	77.9
40–	161
45–	325
50–	544
55–	880
60–	1,364
65–	1,857
70–	2,475
75–79	2,986

which data are available is ages 75–79 years (in 1951–1955) and it is believed that at those ages in Britain cancer mortality is still a fair indication of morbidity. At ages under 55 years the rates observed in 1931–35 have been substituted for those actually recorded for the cohort as inaccuracies in diagnosis are likely to have been progressively more important at earlier periods. For ages under 40 years, the mortality has been derived from the 15 year period 1926–40, to reduce the extent of the random error.

2.3. *Animal data.* It is not the purpose of the present paper to review the available data on experimental carcinogenesis which would, in any case, be beyond the capacity of the authors. Nor is it intended to make an invidious selection of those experiments which are most suitable for the purpose of testing theoretical models. A mass of data is available which, in one form or another, has been used for testing aspects of selected models and some of them will be referred to in section 3 of this paper and by other contributors to the Symposium. It has been noted previously that they have the advantage that precise information is provided about the dose and continuity of application of the carcinogen. It is, however, germane to point out that there is no single series of ex-

TABLE III

INCIDENCE OF BENIGN TUMORS OF THE SKIN OF MICE FOLLOWING BIWEEKLY PAINTING WITH TAR
(Results obtained by C. C. Twort and J. M. Twort and analyzed by Irwin and Goodman [6])

(1)	(2) Animals Living at Beginning of Week			(3) Deaths during Week			(4)	(5)	(6)	(7)
Week	(a) Tumor-less	(b) With Tumors	(c) Total	(a) Tumor-less	(b) With Tumors	(c) Total	Animals Developing Tumors each Week	Animals Exposed to Risk	Tumor Incidence	Cumulative Incidence (%) in Absence of Death without Tumors (Beginning of Week)
0	100		100	0		0				
1	100		100	4		4				
2	96		96	19		19				
3	77		77	18		18				
4	59		59	5		5				
5	54		54	6		6				
6	48		48	3		3				
7	45		45	0		0				
8	45		45	3		3				
9	42		42	2		2	1	41	0.0244	0.0
10	39	1	40	3	1	4	6	37.5	0.1600	2.4
11	30	6	36	0	0	0	2	30	0.0667	18.0
12	28	8	36	0	0	0	1	28	0.0357	23.5
13	27	9	36	0	1	1	4	27	0.1481	26.2
14	23	12	35	0	1	1	2	23	0.0870	37.2
15	21	13	34	1	2	3	5	20.5	0.2439	42.6
16	15	16	31	2	0	2	6	14	0.4286	56.6
17	7	22	29	0	0	0	0	7	0.0000	75.2
18	7	22	29	1	0	1	1	6.5	0.1538	75.2
19	5	23	28	0	2	2	1	5	0.2000	79.0
20	4	22	26	0	2	2	2	4	0.5000	83.2
21	2	22	24	0	2	2	1	2	0.5000	91.6
22	1	21	22	0	0	0	1	1	1.0000	95.8
23		22	22	0	4	4	0	0		100.0
24		18	18	0	1	1	0	0		100.0
25		17	17	0	0	0	0	0		100.0

periments which can be used to test all the implications of any model and that many experiments that would be of value are difficult to employ because the results are expressed only is summary form.

If the results of experiments could be set out in the form demonstrated by Irwin and Goodman [6] for the calculation of the "expectation of tumorless life," the data could be manipulated in any way which the model required. A modified extract from these data is given in table III. The data of greatest general value are perhaps those given in column 6 of the table, which are comparable to the human age-specific mortality rates recorded in table II. For some purposes it may be better to express them as the cumulative incidence in the absence of mortality from other causes (shown in column 7); in this form the irregularity due to small numbers which is obvious in column 6 is apparently smoothed out. It is understandable that experimenters prefer to present their data in the shape of a smooth curve or to consolidate the results in a single figure as, for example, "the expectation of tumorless life." It is, however, unfortunate that when they use a single figure they often omit the basic data or they present them as a cumulative frequency without adequately taking into account the loss of animals exposed to risk through other causes.

It is perhaps worth noting that, despite the small numbers, the experiment analyzed by Irwin and Goodman demonstrated that the incidence of benign skin tumors, following what was effectively a continuous local application, increases approximately in proportion to the fourth power of the age.

3. Mathematical models

3.1. *General.* In the mathematical formulations of the carcinogenic process which have hitherto been published, insufficient attention seems to have been paid to the distinction between an individual cell and a tissue. Most of the models describe processes affecting a cell (or its lineal descendants). Observational data, on the other hand, usually record occurrences in a single tissue (for example, a particular organ of an individual person or animal), and it is not always clear how these observations are to be compared with the predictions of the model. This point will be developed in the next section.

3.2. *Point process for initiation, followed by variable induction period.*

3.2.1. *General.* Most of the models fall into a general category indicated by the heading to this section. It is assumed that initiation takes place suddenly, with a transition probability density $\lambda(t)$ per unit time for each tissue, at time t. The induction period, between the initiation and the appearance of the tumor, follows a probability distribution $F(u)$, with density function $f(u)$. For a constant background or applied stimulus, $\lambda(t)$ is often taken to be constant. When an external stimulus is applied for a short time, $\lambda(t)$ may be assumed to take a relatively high value during the period of application of the stimulus, with a rapid decrease subsequently. $F(u)$ may or may not depend on the external stimulus.

A more precise formulation of the stochastic process may take various forms. For each of the variants discussed below, we give the cumulative probability that at least one tumor has appeared in a tissue before time t (denoted by $G(t)$ with an appropriate subscript), for the situation in which $\lambda(t) = \lambda$ for $0 < t < \tau$ and is otherwise zero.

Variant (i). In each tissue the initiating events form a Poisson process during $(0, \tau)$, and the subsequent induction periods are randomly and independently distributed as $F(u)$.

The probability density per unit time for the appearance of a tumor at time u is

$$g_1(u) = \lambda[F(u) - F(u - \tau)], \tag{1}$$

where $F(x) = 0$ for $x < 0$. The cumulative probability of at least one tumor by time t is

$$\begin{aligned} G_1(t) &= 1 - \exp\left\{-\lambda \int_0^t [F(u) - F(u - \tau)]\, du\right\} \\ &= 1 - \exp\left[-\lambda \int_{t-\tau}^t F(u)\, du\right]. \end{aligned} \tag{2}$$

Note that

$$G_1(\infty) = 1 - e^{-\lambda\tau}. \tag{3}$$

For a continuous constant stimulus, put $\tau = t$. Then

$$\begin{aligned} G_1(t) &= 1 - \exp\left[-\lambda \int_0^t F(u)\, du\right], \\ \lambda F(t) &= \frac{d}{dt}\left\{-\log\,[1 - G_1(t)]\right\} = \frac{G_1'(t)}{1 - G_1(t)}. \end{aligned} \tag{4}$$

If observations are sufficiently extended in time, then, the last part of (4) will tend to an asymptotic value of λ, and such observations should provide estimates of λ and $F(t)$.

For human data, where the clinical stage is relatively short the clinical appearance of a tumor may be approximately represented by death, and the expression at the last of (4) becomes the force of mortality in a life table population subject to one cause of death, namely cancer at a particular site. This is equivalent to the age-specific death rate for the site in question. In general, an upper limit to the age-specific death rate does not seem to be reached during the span of human life. According to the present model, this would imply a distribution of induction period with a median of at least 50 years and a standard deviation of several decades. This result appears to conflict with the observations of latent period in individuals highly exposed to carcinogens, which indicate rather shorter periods on the average. This anomaly suggests that the induction period may be shortened by applying a carcinogen in a high concentration.

Variant (ii). This differs from the previous variant in that all the variation in the induction period is *between* tissues. Each tissue has a characteristic induc-

tion period, constant for all initiating events in that tissue, but varying between tissues with the distribution $F(u)$.

The cumulative probability of at least one tumor by time t is

$$G_2(t) = F(t) - e^{-\lambda\tau} F(t-\tau) - \int_0^\tau e^{-\lambda u} f(t-u)\, du \tag{5}$$

$$= \lambda \int_0^\tau e^{-\lambda u} F(t-u)\, du.$$

The asymptotic result is the same as (3),

$$G_2(\infty) = 1 - e^{-\lambda\tau}. \tag{6}$$

The relationship between $G_1(t)$ and $G_2(t)$ is best seen by considering another variant of the model, which has exactly the same consequences as variant (ii).

Variant (ii)′. The situation is the same as in variant (i), but we consider only tumors arising from the *first* initiating event in a tissue. This is essentially the same as variant (ii), since in each instance the only tumors of which note is taken are those arising from the *first* initiating event, and the induction period varies independently from one realization to another with distribution $F(u)$.

The probability density per unit time for the appearance of a tumor at time u is

$$g_2(u) = \int_0^t \lambda e^{-\lambda z} f(u-z)\, dz = \lambda \int_{u-\tau}^u e^{-\lambda(u-z)} f(z)\, dz, \tag{7}$$

and the cumulative probability of a tumor by time t is

$$G_2(t) = \int_0^t g_2(u)\, du, \tag{8}$$

which reduces to (5). It is clear from the formulation of variant (ii)′ that

$$G_1(t) > G_2(t), \tag{9}$$

since the restriction of attention to the *first* initiating event means that some tumors which are counted in variant (i) are not counted in variant (ii)′.

Variants (i) and (ii) (or, indeed, any intermediate situations) are both quite plausible. Variant (i) would be relevant if the variation in induction period were due to successive realizations of a stochastic process, the parameters of which were the same for each tissue. Variant (ii) would be relevant if induction period were constant for a given tissue (that is, for a given individual) and showed biological variation between tissues. Variant (ii)′ seems implausible, although we have previously followed this approach [7]. Iversen and Arley [8] appear to work with variant (ii)′, although their derivation of the distribution of induction period as the result of a stochastic process suggests that variant (i) might be the more appropriate.

For small λ, variants (i) and (ii) tend to equivalence, as would be expected. As $\lambda \to 0$, for fixed t,

$$G(t) \sim \lambda \int_0^t F(u)\, du = \lambda \int_0^t uf(t-u)\, du, \tag{10}$$

where the subscript has been dropped on $G(t)$.

3.2.2. *Variations in dosage schedule.* The particular situation considered in section 3.2.1 is relevant when an external stimulus is applied for a period τ, and the cumulative incidence of individual tissues showing tumors is measured at different times. Both variants of the model lead to qualitatively similar consequences: from (3) and (6), the final incidence is $1 - e^{-\lambda\tau}$; from (2) and (7) the cumulative incidence at time $t > \tau$ is an increasing function of τ.

To some extent these consequences appear to be borne out by some animal experiments reported by Blum ([9], [10], p. 220). However, it does not seem possible to obtain a good fit to the data by any choice of λ and $F(u)$. There seems to be in practice too sharp an increase in cumulative incidence, when τ increases by relatively little (for example, from 74 to 88 days). This difficulty has been noted also by Arley and Iversen [11], in connection with their rather more specialized model (see section 3.2.3).

Consider now a more general distribution of the external stimulus, a total dose D being distributed in $(0, t)$ with density function $d(u)$ and cumulative distribution function $D(u)$, where $D(t) = D$. Suppose that $\lambda(t) = \kappa d(t)$, and the conditions of variant (i) hold.

The probability density per unit time for the appearance of a tumor at time u is

$$g_3(u) = \kappa \int_0^u f(u - z)\, dD(z). \tag{11}$$

If f is an increasing function, (9) will be a maximum when the dose D is concentrated at $t = 0$. The cumulative incidence of tissues showing at least one tumor is

$$G_3(t) = 1 - \exp\left[-\int_0^t g_3(u)\, du\right] = 1 - \exp\left[-\kappa \int_0^t F(t - z)\, dD(z)\right]. \tag{12}$$

Since F is an increasing function, $G_3(t)$ will attain a maximum value of $1 - \exp[-\kappa DF(t)]$ when the dose D is concentrated at $t = 0$. According to this model, then, fractionation of a dose "forwards" in time will always *reduce* the cumulative incidence at any subsequent time.

A different fractionation problem is considered by Burch [12]. If a total dose D is spread evenly over $(0, t)$, how does the cumulative incidence at time t vary with t? This differs from the previous problem in that the time at which the incidence is recorded is allowed to vary. The cumulative incidence at time t will be

$$1 - \exp\left\{-\frac{\kappa D}{t}\int_0^t F(u)\, du\right\}, \tag{13}$$

which is an increasing function of t. Fractionation of a dose over a longer interval will therefore *increase* the incidence at the *end* of that interval.

In this and the previous section it has been assumed that the distribution $F(u)$ remains constant. A natural development would be to assume that $F(u)$ depended in some way on the dosage function $D(u)$. The possibilities are, of course, wide, and we shall not attempt any general treatment of such a model, although some particular cases will be mentioned briefly in later sections.

3.2.3. *The model of Iversen and Arley.* In a series of papers [8], [11], [13]–[15]

Iversen and Arley investigated in considerable detail the particular case of the present model in which $F(u)$ is a cumulative normal distribution, truncated at several standard deviations below the mean. For a constant applied stimulus, $\lambda(t)$ is taken to be constant, while for a single dose of a chemical carcinogen $\lambda(t) = \lambda_0 \exp(-\alpha t)$. As explained above, the approach is by variant (ii)′ of the model. A number of complicating factors, such as the lethality of the applied carcinogen, are considered. The authors provide an impressive number of instances in which the predictions of the theory agree with observations made in animal experiments. Among these are:

(i) For a single dose, $-\log\{1 - G(\infty)\}$ is proportional to dose.

(ii) For a continuous dose, the mean latent period is linearly related to the reciprocal of the dose.

(iii) The fitted values for the mean and standard deviation of the induction period accord well with values expected if the tumor grew according to a pure birth process and the clinical appearance occurred when the clone size reached a fixed number.

(iv) Experiments of Berenblum and Shubik [16] on the cocarcinogenic effect of croton oil; to explain these results Arley and Iversen [15] develop their basic model to allow a two-stage induction period.

For at least some of the human mortality data, the assumption of a normal distribution for $F(u)$ appears to be satisfactory. For cancer of the stomach in males, for instance, the annual age-specific mortality rates shown in table II are fitted extremely well by (4), where λ is 4,150 per 10^6 per year, and F is a cumulative normal distribution with a mean of about 69 years and a standard deviation of about 15 years.

3.2.4. *Multi-stage induction period.* A number of authors, considering human mortality data, have put forward models in which the induction period consists of a number of different stages, each stage being initiated by a discrete event. Nordling [17] suggested that cell mutations might occur according to a Poisson process, and that a tumor appeared after k specific mutations. Counting the initiating event as the first, this implies that the induction period consists of $k - 1$ stages. Stocks [5] considered a similar model, using a discrete rather than continuous steps of time. He assumed the $k - 1$ stages to form what we have called the larval stage, ending in the pathological appearance of cancer, and postulated a separate development stage of approximate constant length.

Armitage and Doll's [18] model differs from those of Nordling and Stocks in that the changes are supposed to occur in a definite order, the transition probabilities being time-homogeneous but differing from stage to stage.

These models are particular cases of the general model considered in section 3.2.1, and since the variation in induction period is due to the stochastic process taking place, rather than to biological variation from one person to another, variant (i) is appropriate. From (4), the age-specific mortality rate at age t should be $\lambda F(t)$. To evaluate $F(t)$ for the model of Armitage and Doll, suppose that there are N cells (or lines of descent) in each tissue, in each of which the

multi-stage process can take place. The transition probability densities per cell are defined as λ_i/N for the ith event, where λ_1 takes the place of λ in the general formulation above. $F(t)$ is the distribution function of the time up to the $(k-1)$th event in a pure birth process with transition probability densities λ_i/N for $i = 2, \cdots, k$. This process has been investigated by McKendrick [19], Greenwood and Yule [20] and Lundberg [21]. For small values of t,

$$f(t) \sim \frac{\lambda_2\lambda_3 \cdots \lambda_k\, t^{k-2}}{N^{k-1}(k-2)!} \tag{14}$$

(see Armitage [22]),

$$F(t) \sim \frac{\lambda_2\lambda_3 \cdots \lambda_k\, t^{k-1}}{N^{k-1}(k-1)!} \tag{15}$$

and the age-specific mortality rate is

$$\lambda_1 F(t) \sim \frac{\lambda_1\lambda_2 \cdots \lambda_k\, t^{k-1}}{N^{k-1}(k-1)!}. \tag{16}$$

In Nordling's model, where k specific changes must take place in an unspecified order, the age-specific rate (10) is multiplied by $k!$, that is,

$$\frac{1}{N^{k-1}}\, k\lambda_1\lambda_2 \cdots \lambda_k\, t^{k-1}. \tag{17}$$

Fisher and Hollomon [23] suggested that for the development of cancer, mutations were required in k neighboring cells of a tissue. No detailed investigation of this model is possible without specifying which configurations of neighboring cells are to be considered. Presumably, though, if the mutations occur at a rate λ, the cumulative incidence for small t will be proportional to $(\lambda t)^k$, and the age-specific incidence rate will be proportional to $\lambda^k t^{k-1}$. As regards the age relationship, then, this model has similar consequences to the Nordling and Armitage-Doll models.

Various authors, including those mentioned earlier in this section, have investigated the extent to which the pattern of age-specific mortality rates is consistent with (10). The general finding is that for the sites at which mortality rises steeply, (10) is roughly appropriate with $k = 6$ or 7. Stocks finds that with a terminal development stage of about 20 years, the number of changes required is about five. Some of the difficulties in applying these theories to human data have been mentioned in section 2.2.2. In addition it must be remembered that (10) is an approximation only for small t; the expected rates must gradually fall below this approximation as t increases.

Armitage and Doll [18] considered the consequence of allowing one of the λ_i to be time-dependent, and suggested that some features of the mortality data for certain sites could be explained by supposing that one of the λ_i changed either with age (as for hormone-dependent sites) or with calendar time (as for cancer of the lung).

For induced cancer, the dose-response relationship would depend on how many of the λ_i were functions of the dose of the external stimulus. If $j \leqq k$ of the λ_i were

proportional to the dose (supposed constant), the age-specific incidence for small t would be proportional to the jth power of the age. According to Brues [24] there is considerable evidence from animal experiments that $j > 1$, but the evidence on human data is equivocal. The data relating lung cancer mortality to previous smoking habits are consistent with the hypothesis that, in this case, $j = 1$. One of the objections to the Fisher-Hollomon theory is that since all the postulated mutations are of the same type, presumably $j = k$; an incidence rate proportional to the sixth or seventh power of the dose appears to be quite inconsistent with observation.

A two-stage model of rather greater complexity is given by Tucker [25].

3.2.5. *Proliferative induction period.* Models requiring as many as six or seven discrete changes appear rather implausible. Armitage and Doll [7] suggested that the initiating event might impart a selective advantage to the affected cell, giving rise to a clone growing exponentially. Each individual in the affected clone would have a constant transition probability density for a second mutation-like event, which is taken as the pathological appearance of cancer. For purposes of fitting the model to human mortality data, 2 1/2 years were allowed for the combined development and clinical stages.

The suggestion that a mutation might confer a selective advantage to the affected cells had been made earlier by Nordling [17], but his mathematical model took no account of this feature.

More precisely, Armitage and Doll assume a transition probability density, for the first change, of λ_1 per tissue (Np_1 in their notation). The probability density for a "second hit" in any clone, at time t after the initiating event, is taken to be $(\lambda_2/N) \exp(\beta t)$, where λ_2/N and β are used in place of their p_2 and k. Then, the distribution function for induction period is

$$F(u) = 1 - \exp\left[-\frac{\lambda_2}{N\beta}(e^{\beta u} - 1)\right]. \tag{18}$$

If variant (i) of the model is assumed to hold, the age-specific mortality rate at age $t + t_0$, where t_0 is the postulated constant value for the combined development and clinical stages, is given by (4), as

$$\lambda_1 \left\{1 - \exp\left[-\frac{\lambda_2}{N\beta}(e^{\beta t} - 1)\right]\right\}. \tag{19}$$

Armitage and Doll [7] assumed variant (ii)′ and derived (19) as an approximation for small values of λ_1/N.

For the human sites with steeply increasing mortality rates between 30 and 75 years of age, this two-stage model with proliferation appears to give as good an agreement between theory and practice as does the multi-stage model of section 3.2.4. Some more recent studies, using a wider age range, suggest that the agreement is less satisfactory than had been originally thought. Exact comparison with the multi-stage model is, of course, difficult, since (19) holds for all t, whereas (16) is strictly valid only for small t.

The exponential increase of the transition probability density for a second hit, during the proliferative induction period, apparently has much the same effect as several stages with constant transition probability densities. The latter situation, as shown in the last section, leads to the probability density for the final event rising initially according to a power of the time elapsing since the initiating event.

Fisher [26] suggested that during the induction period the clone arising from the cell affected at initiation might grow proportionately to the square of the time since initiation. This is equivalent to assuming a multi-stage process with $k = 4$, and the age-specific mortality rate should be proportional to $(\text{age})^3$. If there are K such proliferative stages during the induction period, the age-specific mortality rate will be proportional to $(\text{age})^{3K}$. As noted in the last section the rates for many sites increase approximately in proportion to $(\text{age})^6$, which would suggest $K = 2$. Burch [12] considers that for the natural incidence of bone cancer and chronic myeloid leukemia, the incidence is approximately proportional to $(\text{age})^3$, suggesting that $K = 1$. It should be noted, however, that the recorded mortality from bone tumors is inflated after age 35 years by the inclusion of a high proportion of cases which are not primary bone tumors and the true incidence increases much more slowly—if it increases at all.

The number of discrete changes involved is two in the model of Armitage and Doll, and $K + 1$ in Fisher's model. For an applied stimulus, the rate of occurrence of any of these could be affected by the dose-rate, and no particular dose-response relationship is necessarily implied by these models.

3.2.6. *Nonproliferative induction period.* Neyman and Scott [27], Kendall [28], and Waugh [29] have recently considered a model in which the first discrete change occurs, as usual, with constant probability density. The affected cell starts a clone of what might be called "intermediate cells," which develops according to a subcritical birth and death process (that is, in which the death rate exceeds the birth rate). All intermediate clones thus eventually become extinct. Each intermediate cell has a constant probability density for a further mutation-like event (or "second hit") which is regarded as the pathological appearance of cancer. During the subsequent development stage, each "second hit" cell develops a clone by a supercritical birth and death process, and the clinical appearance takes place when this clone reaches a certain critical size. In the simplest formulation the parameters of the model are constant; more generally they might be time-dependent.

In this model we could regard the larval stage of the induction period as nonproliferative, since it is during this stage that the subcritical birth and death process is at work. The motivation for this requirement is that the larval stage is identified with a precancerous condition such as a benign tumor or a hyperplastic focus. Shimkin and Polissar [30], [31] found that the number of hyperplastic foci present at various times after a single dose of a carcinogen initially increased with time, and then decreased. This would be expected under the

present model if the "intermediate" clones are recognized as hyperplastic foci as soon as their size exceeds a certain critical level.

We shall not give here any detailed consequences of this theory, which will be described on another occasion in these Proceedings. It is perhaps worth pointing out that, on account of the nonproliferative nature of the larval stage of the induction period, one would expect the rise in the rate of incidence of tumors to be less steep than for a model such as those discussed in section 3.2.5 in which the induction period is one of proliferation. One would conjecture, therefore, that the present model would not easily explain the rapid rise in age-specific mortality rates observed for many sites in man.

Burch [12] considers a model for radiogenic cancer, which postulates two successive chromosome breaks. The initiating event is the first chromosome break (occurring at a constant rate proportional to the dose). The resulting "first-break" cells have a constant rate of suffering a "second-break," but in the meantime are subject to natural elimination and death through lethal radiation hits. (The "first-break" cells are thus at a selective disadvantage as compared with normal cells.) "Second-break" cells are potentially carcinogenic, but again are eliminated through lethal radiation hits. The pathological appearance of cancer takes place after certain biochemical changes have occurred. The author sets up deterministic equations, and obtains an expression for the total number of "second-break" cells alive at a particular time. The transition of a "second-break" cell to a fully cancerous cell is not incorporated in the mathematical model. One consequence of the model which is mentioned by Burch is that for a fixed small dose, D, of radiation applied uniformly over $(0, t)$, the cumulative incidence of live "second-break" cells is inversely proportional to t. This is in contrast to the result given in section 3.2.2, for the case in which the induction period is independent of dose, where the cumulative incidence increases with t. We are not aware of any experimental evidence on this point.

3.3. *Models of gradual development.* In the models discussed in section 3.2, it is assumed that the variation in response of individuals to the same carcinogenic stimulus is largely, or entirely, due to the random outcome of a stochastic process rather than to inherent biological difference. In variant (ii) of the general model of section 3.2.1 the length of induction period is supposed to vary from one individual to another, but here also the time of initiation is determined by a stochastic process.

In contrast to this point of view it might be supposed that the response to a particular environment was a characteristic of the individual. Whether or not an individual tissue showed a cancer after exposure to a single dose would depend on whether its characteristic tolerance was exceeded, and the induction period would be an individual characteristic. Variation in induction period would depend entirely on the homogeneity of the group of individuals.

For a continuous dose or exposure to a constant background, one might suppose that the effects were cumulative. An individual person would show cancer

at a particular site at an age equal to the sum of the age at which his tolerance was reached (at which initiation would take place), and the length of the induction period.

This point of view involves so few quantitative assumptions as to be difficult to refute or confirm. It is, of course, possible to describe the distribution of total survival times in any particular situation, by analogy with the distribution of tolerances in biological assay. The cumulative distribution of survival time for any site of human cancer is obtained by forming a life table population from the age-specific mortality rates. When these rates are low the proportion of deaths below age x will be approximately the sum of the age-specific death rates below age x. For cancer of the stomach in males, the data appear to be consistent with a distribution of survival time such that about 90 per cent of the population have an infinite tolerance (that is, about 10 per cent are susceptible), and the remainder have a normal distribution with a mean of about 80 years and a standard deviation of about 16 years. This estimate is based on only about half of the supposed normal distribution, and clearly many other functional forms would fit equally well. In pharmacology, it is customary to suppose that the logarithm of the dose is approximately normally distributed. It is interesting to note that these data cannot be fitted by assuming a certain proportion of susceptibles, together with a lognormal distribution of survival times.

Blum [9] has put forward a theory of carcinogenesis by ultraviolet light which assumes that any short period of dosage increases the rate of proliferation of certain cells, and the effects are cumulative. The details of his theory are complicated and since this topic is discussed in another paper at this Symposium, further details are not given here. It will be remembered from section 3.2.2 that certain experiments with different dosage schedules are difficult to explain in detail on the general model discussed in that section.

3.4. *Virus tumors.* Certain malignant tumors in animals are initiated by inoculations of virus particles. This situation could be considered within the framework of section 3.2, but the specification of $\lambda(t)$ would depend on some assumptions about the development of the virus population within the host tissue and the mechanism by which the tumor is initiated.

Some progress may, however, be made in considering the dose-response relationship. There is considerable evidence (summarized by Meynell [32]) in favor of the "one-hit" or "independent action" theory of infective systems. According to this theory, each particle of an infective inoculum acts independently and on any one occasion a proportion p may be expected to be capable, alone, of initiating a detectable infection. If p is constant for each host tissue, and each tissue receives an inoculum containing on the average a dose of n particles (the dose having Poisson variation from one tissue to another), then the probability that a particular host is infected will be $1 - \exp(-np)$. If the host tissues vary in susceptibility, so that p has a distribution function Φ, the probability of infection is

$$1 - \int_0^1 \exp(-np)\, d\Phi(p). \tag{20}$$

In general, variation in p tends to flatten the response curve relating the probability of infection to log n.

For tumor-causing viruses, if the cancer initiation is a chance event, brought about by the clone formed by the multiplication of *one* of the original virus particles, the independent action theory would be expected to apply. A "detectable infection" would be interpreted as an infection leading to a detectable tumor. Armitage [33] examined some data published by W. R. Bryan and J. W. Beard. The experiments used the Rous sarcoma virus inoculated into the wings of chickens (each chicken providing one site of inoculation), and the Shope papilloma virus inoculated into sites on the sides of rabbits (each rabbit providing many sites). The results were broadly consistent with the independent action model, with considerable variability in susceptibility of different tissues (that is, animals or sites). The experiments with Rous sarcoma virus suggested that the chickens fell into two groups, differing widely in susceptibility.

Iversen and Arley [14] consider in detail the application of their general theory to virus-produced tumors. They use, however, a deterministic model for the development of the infection, by which each virus inoculum grows exponentially, with the rather unrealistic consequence that each inoculum, however small, will in time produce a tumor.

4. Conclusion

It would be agreeable to be able to conclude that one model was clearly more concordant with observational data than any of the others. Unfortunately, this does not seem possible. One might have expected that suitably controlled animal experiments would provide decisive evidence for or against any particular model, and there is every reason to believe that further light will be shed on the problem by careful experimentation. There are perhaps two main difficulties here. Most of the models which have been considered attribute the variability in response of different animals to the outcome of a stochastic process, and ignore the biological variation in the parameters of this process. Such biological variation must exist, and may be an important factor. It may be reduced by improving the genetic homogeneity of the animals, but in doing so one may detract from the general applicability of the results.

Secondly, to distinguish between different models, it is frequently useful to have information about tumor incidence at very high ages. For human cancer this information will invariably be less reliable than at the lower ages, and for both humans and experimental animals the numbers of observations become rapidly attenuated owing to deaths from other causes. In interpreting human mortality data in terms of the general model of section 3.2, for example, it was noted that the age-specific incidence rates (and hence, approximately, the mor-

tality rates) should be proportional to the cumulative distribution function for the induction period. But reliable data at very high ages are not available, which means that very little can be said about the upper end of the distribution of induction period. In consequence it is very difficult to distinguish between various special instances of this general model, as is noted in section 3.

Some observed phenomena are predicted by the general model, and are common to all the special instances (see sections 3.2.1 and 3.2.2). Some discrepancies are explained when the general model is widened to allow the distribution of induction period to depend on the rate of application of the carcinogen. In particular, such a dependence may be required to explain nonlinear dose-response relationships. Experiments in which the dose schedule is varied should throw useful light on these questions. Blum's data, referred to in section 3.2.2, may be explicable by dose-dependence of the induction period, but since for some groups of animals the dosage periods finish before the tumor incidence rises appreciably, it must be assumed that the induction period is affected by the dosage rate at, or shortly after, initiation.

The ability of different theories to explain the same observed phenomena is illustrated by the fact that many of the proponents of particular models have claimed that their model explains the experimental results of Berenblum and Shubik [16] on the cocarcinogenic action of croton oil. In these experiments application of croton oil, at suitable intervals after treatment with a known carcinogen, produced a much higher incidence of tumors than would otherwise have been obtained. This result would be expected, on the model of section 3.2, if the carcinogen affected the probability of initiation, while the cocarcinogen appreciably shortened the induction period. In particular, in a multi-stage model, the cocarcinogen may be assumed to affect the probability of one or more of the later discrete events. Iversen and Arley [15], in considering these experiments, develop a more general model than that described in section 3.2.3, in which more than one mutation-like event is required.

In summary, we doubt whether the available observational data provide clear and consistent evidence in favor of any particular model. Further elucidation is likely to come either from direct biological evidence of a nonquantitative nature, or from quantitative experiments, carefully designed and reported, perhaps on a larger scale than is usually undertaken at present.

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