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SOME PROBLEMS IN THE STUDY OF CANCER IN MAN

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Cancer research is now unavoidably divided into two sections: (a) *fundamental*, which looks for an answer to the question "Why, and how, does a cell divide?"; and (b) *empirical*, which seeks to identify carcinogenic factors which we can avoid. The first of these has passed wholly into the field of physics and chemistry and requires the most refined methods, both technical and theoretical, of those subjects. To many persons, distressed by the mortality from cancer, progress may seem very slow, but they should remember that the full application of biophysics to the problem is of very recent growth, and that whole areas of knowledge which we do not yet possess may be required for success. No doubt Wellington could have saved a great number of British lives at Waterloo by the discreet use of an atomic bomb of very modest dimensions before the armies engaged, but the requisite technique simply did not exist.

The present paper brings together some of those questions in purely empirical cancer research which seem to be ready for further inquiry. However anxious we may be to simplify the problem of cancer, we must recognize that it is inherently complex because the animal body itself is complex. Even when a reasonably satisfactory answer can be given to the fundamental question "Why, and how, does a cell divide?" the application of this knowledge to the very peculiar distribution of cancer by sex and organ must present many problems.

Cancer of the Cervix and Circumcision

The view is now advocated that the association between cancer of the cervix and non-circumcision of the male (Wynder *et al.*, 1954; Wynder, 1955) is due to transference of carcinogenic smegma in the act of intercourse, a process which would be identical in nature with a mouse-painting experiment. Whatever one may think of the likelihood of this explanation, it certainly offers a remarkable instance of the specificity of carcinogens for different tissues. In England and Wales in 1945 there were 4,039 deaths attributed to cancer of the uterus other than of the corpus; if any large fraction of these was due to application of smegma it is remarkable that in the males, where the contact of this material with the epithelium is intimate and continuous, there were only 132 deaths from cancer of the penis, though some other cases may have been cured by surgery.

A causal connexion between cancer of the cervix and non-circumcision was suggested first by W. Sampson Handley (1936), who wrote of "marital infection with the sub-preputial flora" and seemed to think of this factor as sufficient in itself and as already proved. Such certainty is quite unwarranted, because we do not know (1) that the

vaginal flora is in fact altered, although this question is quite accessible to investigation; or (2) whether any such alteration is pro- or anti-carcinogenic.

The use of a condom protects the cervix from any transfer of carcinogenic material from the male more effectually than does any other method, and in theory provides the ideal experiment for settling this question, but actually it is difficult to ascertain the constancy of the practice over a number of years.

Cancer of the Cervix in Jewish Women

The low incidence of cancer of the cervix in Jewish women is established by a number of investigations. The literature up to 1947 was summarized (Kennaway, 1948) and much confirmatory material has been published since then (Wynder *et al.*, 1954.)

Various possible explanations have been suggested, of which one is the Jewish law relating to menstruation. A section (Niddah) of the Talmud, consisting of 10 chapters, forbids coitus during the flow, and for not less than five days, and for seven days afterwards, hence the whole period of abstention is $n+7$ days and n is never less than 5. Under normal conditions, abstention for 12 days would allow resumption near the time of ovulation, of which process those who laid down this rule of course knew nothing (for further details see Kennaway, 1948).

To assume that the law of Niddah is, for all practical purposes, obsolete, is easy, and this solution of the question is often put forward and sometimes seems to be welcome. But such matters of purely private conduct need very careful inquiry. The lack of any adequate investigation from Jewish sources is perhaps not very surprising. To the orthodox believer all such laws are the direct expression of God's wisdom, and human approval or disapproval of them is wholly irrelevant, while to one of the modern school they are elements of a primitive religion with which he may not wish to be associated. But any attempt to gain from this source more knowledge is surely in no way inconsistent with the belief that the practice is of Divine institution. All recent work upon cancer of the cervix (the literature is reviewed by Wynder *et al.*, 1954) indicates that marriage, apart from child-bearing, and especially early marriage, increases the liability, while the celibate life of nuns (Gagnon, 1950) gives protection. By "marriage" in this sense one means, not any civil or religious state, but coitus. Between these two extreme conditions of early marriage and virginity there is surely the bare possibility that the partial abstention enjoined by the law of Niddah gives partial immunity. At any rate, the question is worth investigation; and why can it not be settled one way or the other in the next year or two?

Any idea that the law of Niddah is now an almost forgotten matter, of merely antiquarian interest, is simply

untrue. In London, at any rate, a Jewish girl whose engagement is announced in the Press receives from one or other of certain Jewish societies a simple, practical, and forcible statement of the law, and often this is her first acquaintance with it. How far these instructions are obeyed is of course another matter altogether, but those to whom they are of most concern cannot be ignorant of them even here at the present day.

There are at least two methods of investigating this question—namely, to ascertain (1) the proportion of women who obey any part of the relevant law in a Jewish community in which the incidence of cancer of the cervix can be ascertained, but the inquiry about obedience to the law must be a genuine one, not mixed up with any assumptions or general impressions; (2) the personal history of any Jewish woman who develops cancer of the cervix. This would appear to be the simplest and quickest method of approach, because the results in, say, a dozen cases might show whether this line was worth following, although such a number would be considered quite inadequate statistically. This method has been applied by Wynder *et al.* (1954), who obtained the following result (Table I).

TABLE I.—Observance of Talmudic Law in 20 Cases of Cancer of the Cervix in Jewish Women (Wynder *et al.*)

Class	In	Days' Abstinence after Menses
Class A:	In 10 women	0
" B:	" 5 "	5, 4, 3, 3, 2
" C:	" 5 "	7

One may suggest that the value of these 20 cases as evidence is not uniform. Of the 10 women who practised no abstinence, 7 had intercourse with more than one partner, and hence one can believe that they were not scrupulous in obeying any part of the Talmudic law; whether the statements of the 5 women of Class C, that they observed the seven-days rule, are equally convincing, may be a matter of opinion. All the women in C and 3 of the 5 in Class B had one partner only. Wynder *et al.* (1954) ignore this aspect of the matter altogether and discuss only the data relating to age and circumcision, while Wynder (1955), in his most recent paper, says, without quoting any tabulated data, "Twenty Jewish cervical cancer cases do not suffice for statistical comparison, but they seem to be in line with the controls. Five of the 20 patients in this group did not abstain after menses." He does not explain the reduction from 10 to 5 of the non-abstaining cases. The relevant passage in his summary, "The abstinence period practised by orthodox Jewish women after the end of menses is not believed to be the basic factor accounting for the low incidence of cervical cancer among Jewish women," does not encourage further investigation.

Table I certainly indicates that further inquiry is very desirable. After all, one may not get a quite clear-cut result because all cases of cancer of the cervix may not have the same cause, just as all cases of cancer of the lung are not due to smoking. In any case, this one series of 20 cases cannot be held to settle the matter, and material for further inquiry must be available in Jewish practice in London. In both inquiries, (1) and (2) above, the truthfulness of the replies is, of course, vital, and it is therefore all-important that the women should not regard the questions as a moral inquisition. Probably the best interviewer would be a Jewish woman doctor.

Cancer of the Lung in Non-smokers

This process is of great importance as the background upon which the effects of smoking are superimposed. The number of deaths in both sexes attributed to cancer of the lung in England and Wales annually is now about 15,000. Doll (1953) considers that about one-fifth of these deaths—that is, about 3,000—are not due to tobacco. The consumption of tobacco, especially in the form of cigarettes, has increased considerably in the last 30 years, and hence any form of cancer due to smoking would be expected to

increase also at some later period. We do not know the cause, or causes, of the 3,000 cases independent of tobacco, and therefore we have no reason to think that this factor has increased. Even if it has increased, it is extremely unlikely that it has done so in close parallelism to the increase in the consumption of tobacco. As we know nothing to the contrary, we may assume for the moment that this factor has not altered in, say, the last 30 years.

If this were so, the unknown factor would have produced about 3,000 cases every year during this period. But as recently as 1935, when the number of deaths was 3,195, this source would have supplied the whole number which occurred, and, proceeding backwards, the total falls to 612 in 1922 at the beginning of the 30-year period (Fig. 1). It is

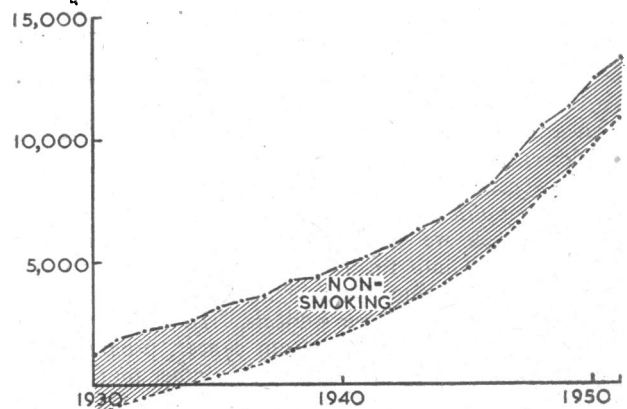


FIG. 1.—Deaths from cancer of lung. Males and females. England and Wales.

of course quite easy to invoke "defective diagnosis" as the sole explanation of any such process, whatever its magnitude or time-relations may be, and to attempt no further investigation, but any assumption that such errors are exactly adequate numerically for this purpose is purely arbitrary. The unknown factor may be (a) extrinsic or (b) intrinsic. (a) It is unlikely to be one of the known occupational factors which are carcinogenic to the lung (chromates, arsenic, nickel, asbestos, radioactivity), because these affect only small numbers of persons, chiefly of the male sex. (b) The absence of any sexual difference and the lack of any correlation with density of population suggest an intrinsic factor. The identification of this factor would be of very great interest.

No doubt the crude data shown in Fig. 1 require careful analysis in view of the considerable changes in the age structure of the population which have taken place in the last 30 years, but that is a matter for statisticians.

The proportion of non-smokers is important when the consumption of tobacco in different classes or countries—for example, Britain and Finland—is being compared. Thus in the latter country women appear to smoke very little, and hence the consumption "per head" falls very largely upon only one-half of the population.

In the long run it may appear that this sorting out of the cases not due to tobacco is the most valuable part of the immensely important contribution of Doll and Bradford Hill, and others, to cancer research; this same unknown factor may be the cause of malignant growth in other organs also. "We can avoid the one factor, tobacco, if we wish, because we know what it is; we cannot avoid the other.

Deaths Attributed to Cancer of the Lung in Women

In England and Wales the increase in 1953 amounted to only 11 cases (Registrar-General, 1954), whereas the deaths of males showed an increase of the usual amount (891 cases). Of course, this halt may not persist, but, if it does so, the problem of the factors, perhaps first active many years ago,

which are concerned in this change will be very attractive, or, if one is then still expected to think that a very large part of the increase in deaths attributed to cancer of the lung is due to improved diagnosis, an explanation of this sexual difference must be found.

Histological Characters of Cancer of the Lung

These cancers show about five different types, which may differ in aetiology. Hence when one compares the total incidence of cancer of the lung upon different populations and countries one may be concealing important differences in the proportions of these types. Recently Kreyberg (1954) has emphasized the importance of this question. The practical difficulty is to obtain data from large numbers of unselected cases in which the diagnosis has been made by competent histologists, and some experienced observers are doubtful about the value of such classifications on the ground that more than one type may occur in the same lung.

Systemic Effects of Tobacco

The obvious method by which tobacco smoke can have a carcinogenic effect is by the arrest of the droplets of which it is composed upon the bronchial mucous membrane. But the inspiration of this smoke has such powerful systemic effects that one wonders whether these may possibly play a part also. The discharge from the posterior pituitary has so strong an antidiuretic effect (Walker, 1949) that the comment has often been made that one wonders how some cigarette smokers pass any urine at all (Fig. 2).

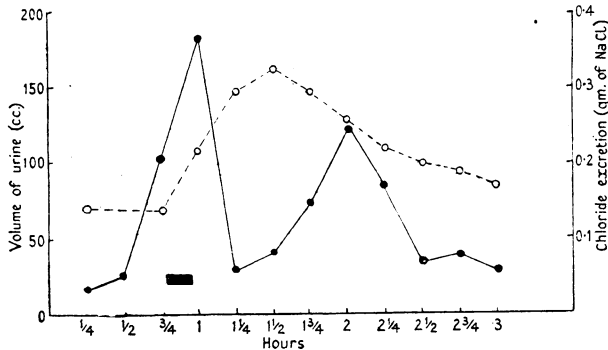


FIG. 2.—Systemic effect of tobacco. The subject drank 900 ml. of water at zero. He emptied his bladder at 15-minute intervals. The continuous line shows the volume of urine excreted. After 45 minutes he smoked one cigarette, which produced the inhibition shown in the graph. The broken line shows the total chloride excretion. Note the rise in total chloride coincident with the inhibition (Walker, 1949). Reproduced by permission of Dr. Walker and the *Quarterly Journal of Medicine*.

This secretion of the posterior pituitary is also broncho-constrictor, and this action might slow down the inspiratory current and thus favour the deposition of particles, but so far no such effect of smoking has been demonstrated. Dr. H. G. J. Herxheimer, of University College Hospital, London, very kindly subjected two smokers to a test with his apparatus which measures resistance to expiration, and could find no effect. But possibly other systemic effects might be worth consideration.

Amount of Cancer

When the occurrence of cancer in different populations is compared, the incidence may be found to fall more or less upon one or another organ, while the total number of individuals remains about the same whatever the organ or organs chiefly affected. There seems in these cases to be something that may be regarded provisionally as an "amount" of cancer, and the anatomical distribution of this "amount" is variable (E. L. and N. M. Kennaway, 1937).

"There appears to be a general law that when in a given population the incidence of cancer in one particular organ

is markedly increased as compared with another population, there is then a compensating decrease in the incidence of cancer in a number of other organs. As a result, the incidence of cancer in different populations, whether of the same sex or not, may represent a very different distribution over the various organs or tissues, but the sum total—the total incidence of cancer—remains on an even level. This phenomenon shows that the development of malignancy in a given site, although in itself a strictly localized process, is conditioned by factors lying outside the site, which may therefore be called 'general' or 'systemic' factors" (Cramer, 1931).

This phenomenon was described first by Snijders and Straub (1924) in Sumatra; a small selection from their results is given in Table II.

TABLE II.—Incidence of Primary Cancer of the Liver in Sumatra, and in England and Wales (Snijders and Straub)

	Javanese Men	Corresponding Group from Dutch Statistics	Javanese Women	Corresponding Group from Dutch Statistics
Mortality from cancer per 100,000 per year	26.6	24.3	25.4	24.5
Primary cancer of liver % of all cancers	84	England and Wales, 1931 4.8	22.2	England and Wales, 1931 4.7

Perhaps the simplest instance of the "amount" of cancer is afforded by a comparison of cancers in the two sexes in the same country (Table III).

TABLE III.—Deaths from Carcinoma, 1940-2. England and Wales (General Register Office)

Males		Females	
Cancers of male reproductive organs ..	7,172	Cancers of female reproductive organs ..	38,916
Scrotum, prostate, testis, penis, etc.	7,009	Uterus, ovary, tubes, vulva, vagina, etc.	18,867
Breast	163	Breast	20,049
Other organs	82,730	Other organs	58,090
Total	89,902	Total	97,006

Excess of cancers in females .. 7,104

For instance (Table III), the total deaths from carcinoma in males (89,902) and females (97,006) show a difference of only about 7%, yet the latter total includes 38,916 deaths, or 40% of the whole, from carcinoma of organs peculiar to the female, among which organs the female breast, being capable of lactation, must for the present purpose be reckoned.

One wishes that statisticians would some day examine this matter and tell us to what extent the figures merely illustrate the fact that a person who dies of a disease A does not die of a disease B. But it is difficult to believe that that is all that can be said about it.

Localization of Malignant Growth

This extremely important subject seems to attract very few investigators, probably because it does not promise to yield quickly that "something to publish" which assures renewal of annual grants and is the bane of cancer research.

Cancer of the breast causes the death of about 7,300 women in England and Wales per annum. If one omits the other cases cured by surgery and divides this number by 365, one finds that every day only about 20 of the 13 1/2 million women aged 30 and over begin to develop this form of cancer. Moreover, in the great majority of these, the disease begins in one of the two breasts, and at one small area in this glandular organ of considerable size. Hence the importance of localizing factors is obvious, but we know hardly anything about them. In recent years much has been learned about hormonal factors in relation

to the breast, but these are distributed in the blood stream and there is no apparent reason why their action should be localized. Such considerations apply also to some forms of cancer of the lung where substances introduced and dispersed with the inspired air represent the hormonal factors in the case of the breast.

Possibly every case of cancer arises from the conjunction of a number of factors, as yet unknown to us, at one spot. Those who think that the carcinogenic action of, for instance, cholesterol (Hieger and Orr, 1954) can be ignored because this compound is "a normal constituent of the body" show little comprehension of biochemical matters. The highly dangerous properties of another normal constituent—namely, potassium—are kept under control only by the balance of other factors.

Incidence of Cancer in Town and Country

A number of investigations have shown, with varying degrees of distinctness, a higher incidence of various forms of cancer among town dwellers. In seeking for a reason, the fact that better methods of diagnosis are more accessible in towns is always easy to invoke and difficult to assess. Where the respiratory tract is concerned one must of course consider atmospheric pollution and exposure to soot containing at least one carcinogen—namely, 3:4-benzpyrene (Stocks, 1936, 1953; E. L. and N. M. Kennaway, 1951; Curwen *et al.*, 1954). But does this latter factor affect any other parts of the body? Cancer of the scrotum is rare in agricultural workers and is almost unknown in those social classes who wash most (E. L. and N. M. Kennaway, 1946). Thirty years ago the suggestion was made that "it would seem possible that cancer of the scrotum is influenced by exposure to coal-smoke—in other words, possibly all town dwellers are in some very slight degree liable to "chimney-sweep's cancer" (Kennaway, 1925). A complete survey is required of the incidence of every form of cancer upon dwellers in rural districts, and in the various grades of urban areas, in which every effort is made to discriminate between the effects of better diagnosis, and of town smoke; the latter factor is remediable by methods already in existence. Probably various carcinogens, with the exception of sunlight, are more abundant in towns and their actions may summate, a process about which we know very little; the latest contribution on this question is that of Cloudman *et al.* (1955).

Cancer and the Consumption of Milk

Cow's milk contains a carcinogenic factor in the non-saponifiable fraction, as do various human organs (Hieger, 1949), and, as a constituent of diet, has a protective action against some forms of cancer (Hoch-Ligeti, 1952). The consumption of milk by man shows great differences in different countries, dependent upon a variety of factors such as the character of pasture, the tsetse fly, sexual and social taboos and conventions, and so on. In some parts of Africa the numerous cattle are not regarded as sources of milk, nor of meat, but as currency, especially for the purchase of wives. In some areas milk is taboo for men, as it was in effect in this country not very long ago (Kennaway, 1951). The numerous travellers in Tibet who write books always emphasize the abundance of Yak butter, while Australasia had no source of milk until the nineteenth century. Even countries in Europe show considerable differences in this respect; thus the daily consumption of milk is high in Finland (Kennaway, 1954), being about 1.34 pints per head as against 0.72 pint in the United Kingdom.

Anyone wishing to make a literary investigation of this matter would find a great quantity of data scattered through official and other publications; the results might or might not show any correlation with any forms of cancer, and could of course be used in the study of any other diseases also. Two valuable publications are those of the Food and Agriculture Organization of the United Nations (1952, 1953).

A Suggestion

Cancer research, like other branches of science, is tending to be buried under its own literature. Those whose business it is to attempt to keep a watch upon this literature know that many investigations are reported which appear to promise further results, and yet, in say ten years' time, if they are remembered at all, they are found to have had no progeny. This may be because they are inherently infertile, or because the investigator has been diverted to other matters which appear more productive of results and annual grants: these forgotten researches are hidden, like coelacanths, beneath an ocean filled by other developments. Surely some persons should be appointed to pick over the literature of, say, the last 25 years in the light of later knowledge and to seek for anything worthy of resuscitation; they should hold a quite definite appointment with good remuneration, should be under no obligation to produce anything, and should be trusted to carry on their work efficiently without any compulsion to write endless reports about it. They will reject many researches because the technique was inadequate at the time or is shown by our later knowledge to have been so; but now and then something useful may be disinterred.

In 1945 J. C. Mottram described a greater yield of tumours of the skin of mice from 3:4-benzpyrene when applied at midnight than when applied at midday; he attributed this difference to greater mitotic activity at night, and did not consider any other possible diurnal differences in metabolism. This result indicates that the conditions during the first few hours after application determine the yield of tumours during the second and later months. At the present time research on cancer is much concerned with such periods of incubation. Thus, Nielsen and Clemmesen (1954), in a very short paper of great interest, have plotted figures for the mortality from cancer of the lung in 1950 against those for the consumption of cigarettes in 1930. Mottram's result is of such importance that one wonders whether the experiment has ever been repeated. He used only 6, and 24, mice in his two experiments, and made the day, and night, pairings on opposite sides of the same mouse, which is not the only possible, and perhaps not the best, procedure. A very experienced worker with whom I have discussed the result is very dubious about it. Those who knew Mottram, who died in 1945, will agree that, though he was far from infallible, his numerous ideas were always interesting; at heart he was much more a zoologist than a pathologist.

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