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REVIEW OF RECENT CANCER RESEARCH

BY

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Director of the Laboratory, Imperial Cancer Research Fund, London

MIDDLETON GOLDSMITH LECTURE

1912

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LECTURE I.

STATISTICAL AND COMPARATIVE INVESTIGATIONS

The recent advances made in our knowledge of cancer may be grouped together according as they have been obtained by statistical or by experimental methods. In this first lecture I shall direct your attention to the results which have been obtained by improving the national statistics of England instead of taking a separate cancer census as was done in Germany and other countries, and to certain other statistical observations. In the second lecture I shall discuss the results of experiments.

A few general remarks are necessary to introduce the statistical details. It is essential that the great frequency of cancer should be borne in mind, because this of itself explains why aggregations of cases are bound to occur. Cancer is so frequent in England that one out of every seven women and one out of less than every eleven men above the age of 35, ultimately dies of it. On this basis it is possible to calculate[2] how often one, two, three, or more, cases of cancer may be expected in a family. Of 100 families each of six members, 3 males and 3 females, no case of cancer would be expected in 51, one case would be expected in 36, two cases in 11, and 3 or more cases in 2 families. Of 100 families of eight members, four women and four men, no case would occur in 41, one in 39, 2 in 16 and 3 or more in four families. In 100 families of ten members, five men and five women, only 33 would be expected to escape altogether, whereas there would be one case in 39, two in 20, and 3 or more in eight families. Moreover, the disease is ten times as frequent at 70

[1] Middleton Goldsmith Lectures delivered before the New York Pathological Society, October 2 and 4, 1912.

[2] Calculation made on the basis of 1 in 8 and 1 in 11 respectively.

as at 35 years of age; therefore similar calculations made for age periods other than 35 would show a corresponding greater liability than the averages set forth above. Hence aggregations of cases of cancer to have any significance at all must occur with a frequency which removes them from all possibility of their being merely what would be expected owing to the great frequency of the disease. In the course of years it is quite natural that a number of cases should occur in a village, a street, a house, or even a family which has inhabited the same house for generations, without the numbers necessarily meaning anything more than what was to be expected according to the theory of probabilities. This criticism applies without exception to all statements as to cancer houses, cancer streets, and cancer villages, which have been adduced as evidence that cancer is infective, although I do not wish to be understood as denying that cancer or rather certain forms of it occurring on different parts of the body, may, and actually do, vary in different areas.

As is apparent from the figures I gave of the relative liability of males and females above 35, the relative frequency of cancer is influenced very largely by the relative proportions of the two sexes and the respective numbers of each sex living at each age-period. If a curve be constructed of the mortality from an infective disease, *e. g.*, tuberculosis, and regard be paid to the different age-periods, it is at once evident that the sacrifice of life is already high in the early years of life. After a fall the curve rises till about middle-age and thereafter falls to the end of life. The curve is very similar for the two sexes, although higher throughout for males, as also in the case of typhoid; but throwing the two sexes together into one curve does not materially modify it.

If similar curves be constructed for cancer the appearances are markedly different. If both sexes are lumped together and age-periods are regarded, cancer is of no importance as a cause of death till 25–35; but thereafter the curve rises progressively up to the end of life. If the sexes be considered apart the curves diverge widely, that for women being the higher. At birth cancer is more common than at 10–15 years: this applies both to car-

cinoma and sarcoma and can be brought into connection with developmental anomalies in which complicated tumours, or sarcomata, more rarely carcinomata, have arisen. From the 20th year onwards the curve for each sex rises progressively, and likewise both for carcinoma and sarcoma. The old teaching that sarcoma was a disease of youth is untenable; sarcoma is relatively more frequent in youth than is carcinoma, but both become more frequent in a parallel manner as life advances. The old teaching, now shown to be erroneous, was due to the statistical fallacy of generalising from hospital statistics which have no relation to the actual facts of population, its sex and age constitution.

The curves in which all cases are thrown together, although they give valuable information, conceal very important facts which are only revealed when curves are constructed not only for each sex at the several age-periods, but also for each organ or site of the body. Then the greater frequency of cancer in women is seen to be due to cancer of the breast and uterus. It is also evident that the relation between age and mortality is different for the different organs but parallel for the same organ in the two sexes. This similarity is illustrated by the extreme example of the cancer of the breast so common in women, so rare in men. The curves are parallel and rise to the end of life in both sexes; the same obtains for the liver, skin, rectum, lip, and face. If different organs are compared, *e. g.*, breast and uterus, the curve for the uterus attains only half the height of that for the breast according to age, although there is a greater total mortality from cancer of the uterus than for any other single organ. This difference is in part explained because cancer of the uterus becomes a frequent cause of death, and therefore causes more deaths at earlier ages than does cancer of the breast. Nevertheless, the curves bring out real differences in the susceptibility to cancer at different ages in the two organs; whereas the curve for the breast rises to the end of life, that for the uterus flattens after 55 and falls progressively after 65. Similar differences exist also for other organs; skin, lip, and face have typical curves, rising to the end of life, which stand in sharp contrast to the equally typical curves for the tongue, liver, intestines, stomach, which attain a maxi-

mum followed by a fall. For some organs there is evidence of two maxima. These differences in the age incidence of cancer for different parts of the body demonstrate that in any discussion of the greater frequency of cancer in one area than in another, it is essential that the different organs and sites of the body be considered apart and not all lumped together.

The preceding considerations show the importance of age and the difference in its influence for different organs. Even if statistics alone are not able to explain this phenomenon, they do permit of the inference that probably more than one cause is operative in the etiology of cancer. I shall have to revert to this subject when I come to consider experimental methods. Before leaving this subject however, it is important to emphasise that this law of age-incidence is a biological law which holds both for long and for short-lived animals; it is as fully applicable to the mouse, which rarely lives three years, as it is to man. Great as is its statistical importance, its biological significance has even a greater heuristic value. I have applied it to the several organs of the human body, where, for example, the short-lived chorion represents the one extreme and skin the other, and together with Murray have urged that it must be taken account of in any satisfactory explanation of cancer. It would appear that it is not age or senility of the individual that is an important contributory etiological factor, but rather senescence of the individual tissues. Further discussion of its significance appears profitless, till it is determined whether the fall which occurs for some organs is a real fall or not.

With the exception of diabetes, cancer alone of all causes of death exhibits a constant increase in the number of deaths recorded. This phenomenon is a characteristic feature of mortality statistics wherever they are compiled throughout the world. In England, where reliable statistics are available for the longest series of years, the death-rate per million living has risen from 500 in 1860 to 1,060 in 1909, the corresponding figures for males being from 200 in 1860 to 820, in 1909. Stated otherwise, of women above the age of thirty-five, one in 12 was recorded as dying of cancer in 1889, but one in seven in 1909, and of deaths

of men one in 21 in 1889, but one in almost 10 in 1909. Stated in this way or exhibited in curves (Figs. 1 and 2) constructed on this basis the increase in the number of deaths recorded is both astonishing and alarming and has alarmed both the medical profession and the public. But they are crude statistical methods.

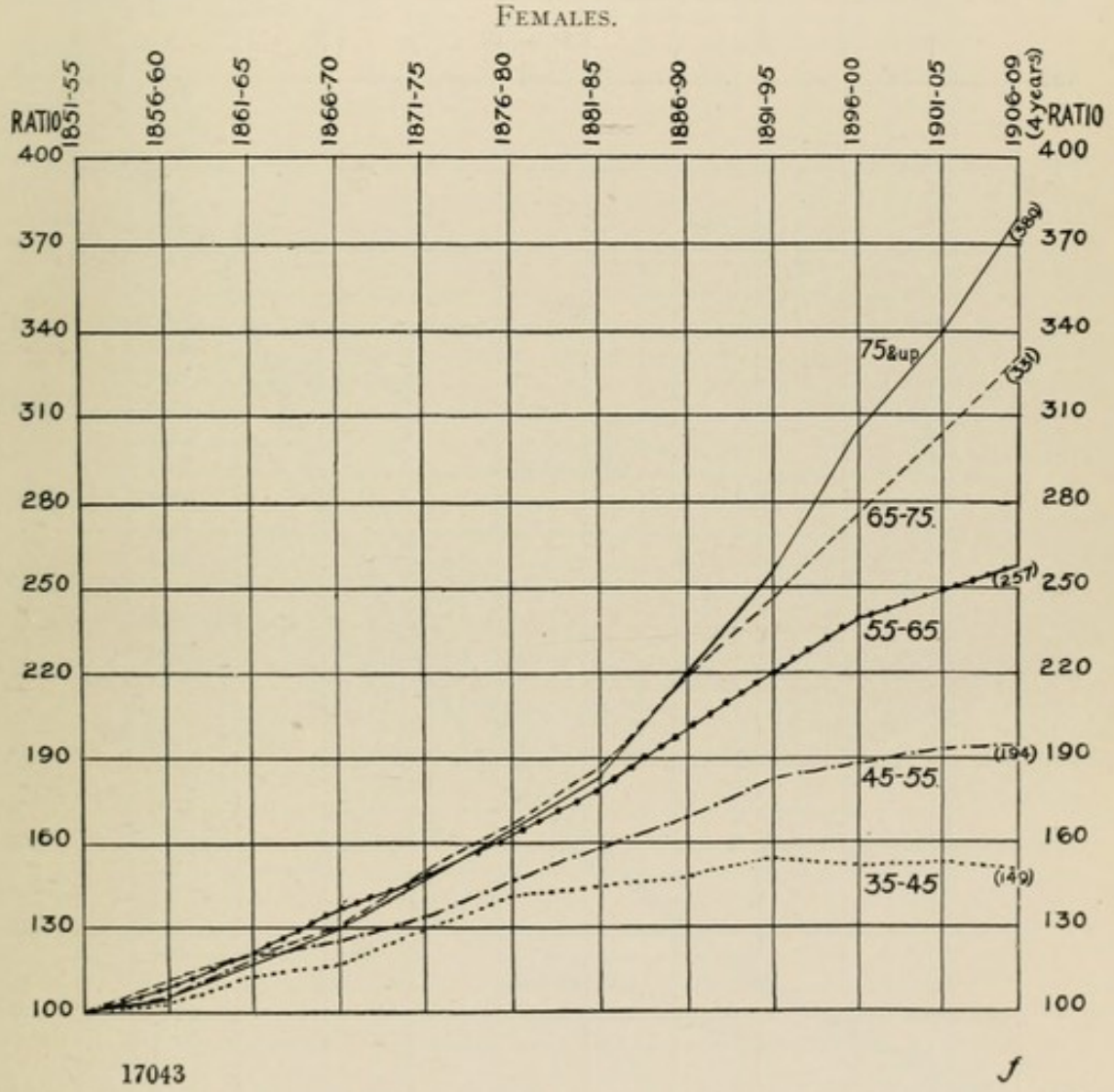

FIG. 1.—ENGLAND AND WALES.—Cancer. Ratio per cent. of mortality at several age-groups in quinquennia since 1851–5 to the mortality at the same age-groups in 1851–5.

From time to time attempts have been made to explain the increase by the fall in infant mortality, the fall in mortality from tuberculosis, and infective diseases in general. If this were so, then there should be no increase if comparisons were made be-

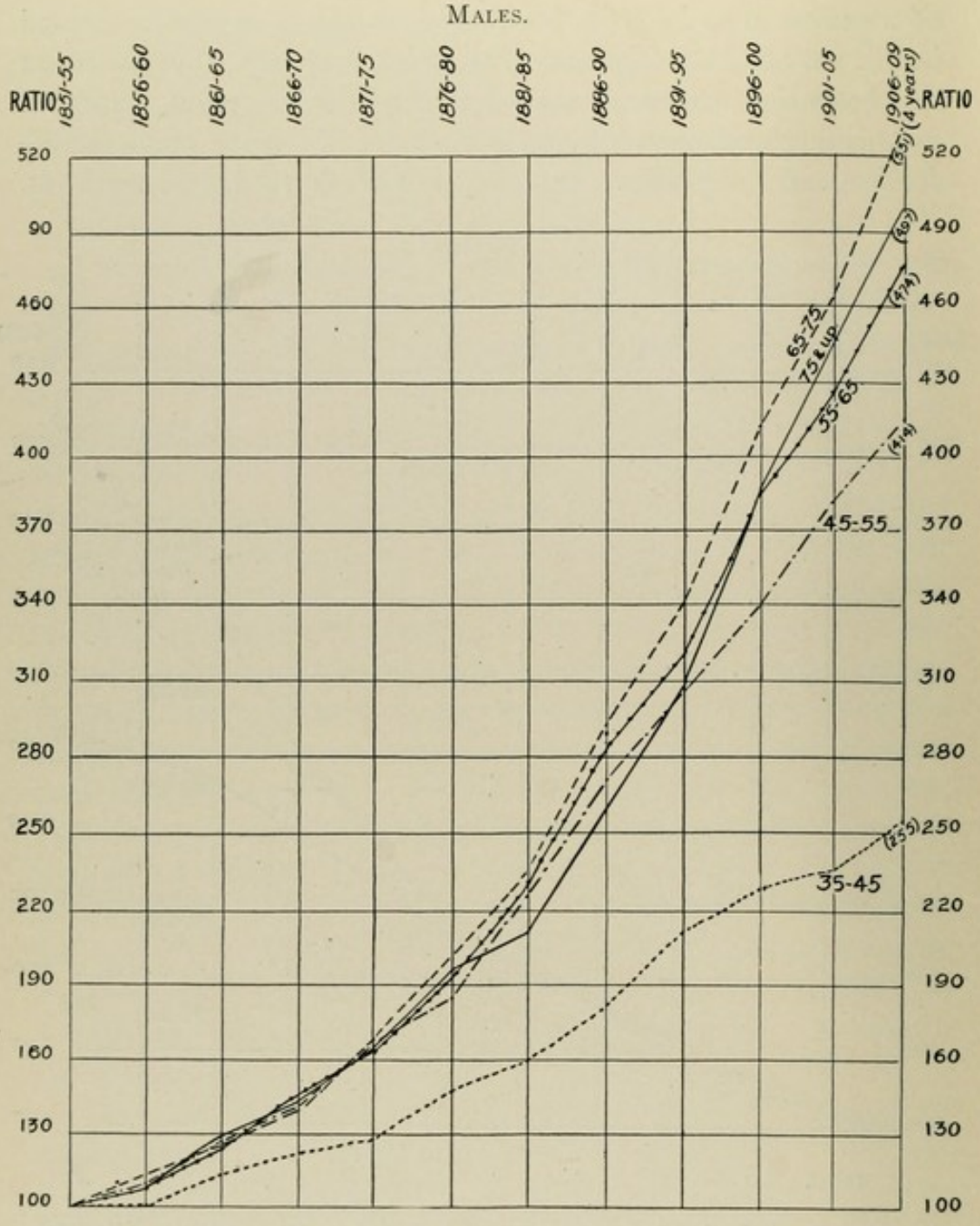

FIG. 2.—ENGLAND AND WALES.—Cancer. Ratio per cent. of mortality at several age-groups in quinquennia since 1851–5 to the mortality at the same age-groups in 1851–5.

tween a million living at each age-period years ago and to-day. However, when this is done there is still an increase, and as a matter of fact such an explanation involves the grave statistical

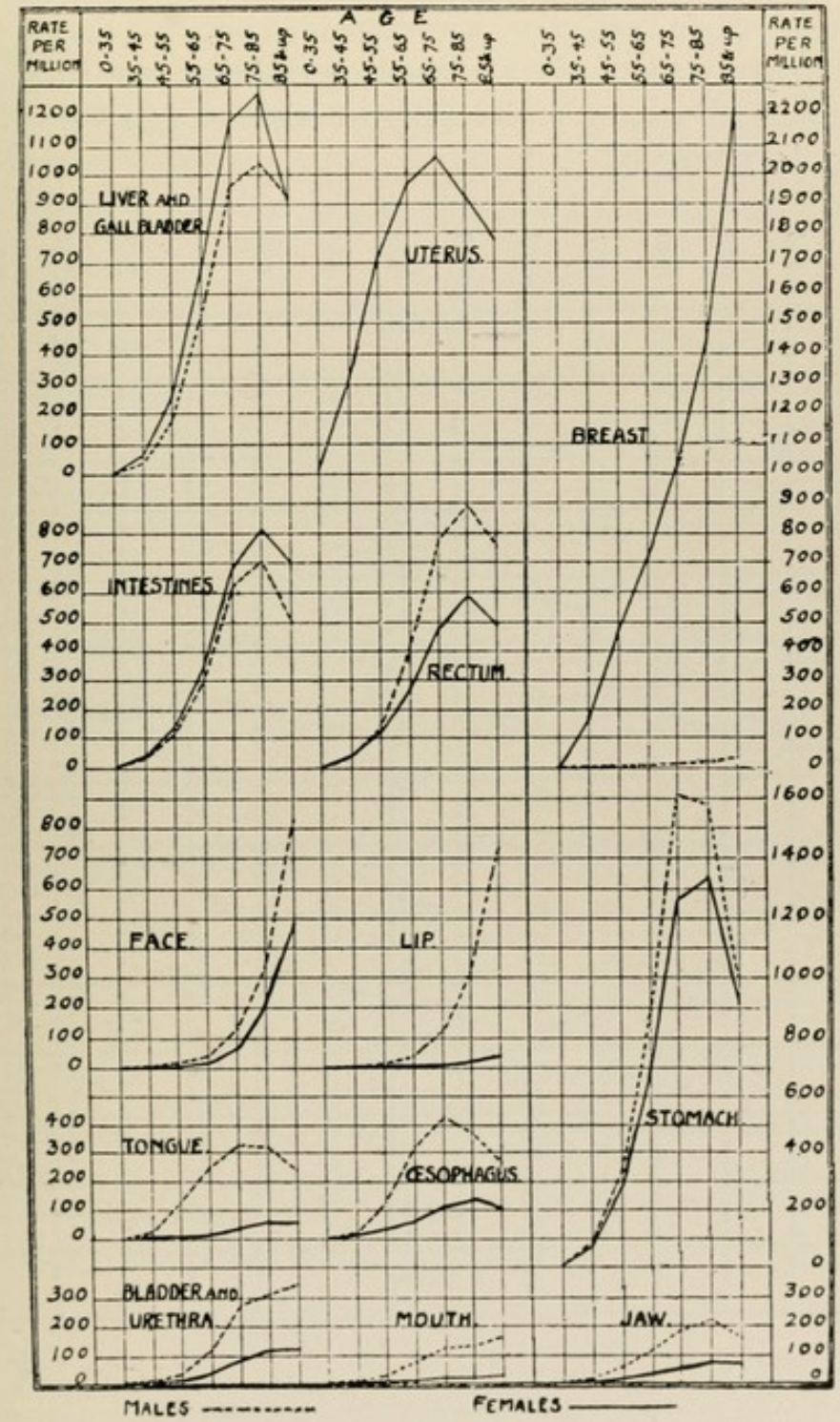

FIG. 3.—ENGLAND AND WALES.—Cancer. Age and sex mortality from cancer of various parts of the body. 1901–9.

error of confounding death-rates with total deaths. It is quite true more people reach the cancer ages but the question is, Do a higher proportion of them die of cancer than did fifty years ago? A further question is: Why has the increase been greater in men than women?

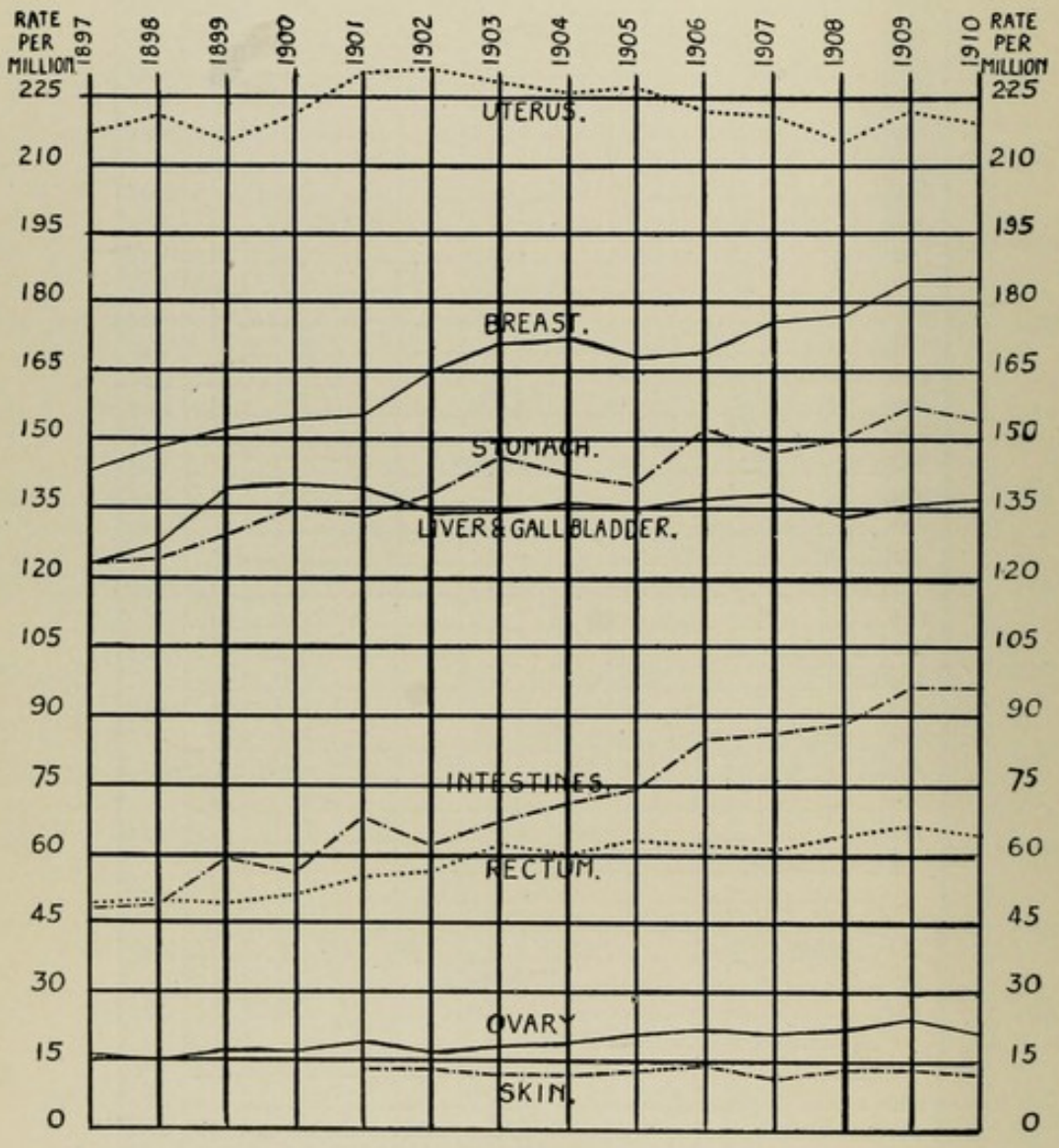

FIG. 4.—ENGLAND AND WALES.—Cancer of various parts of the body; mortality at all ages, 1897–1910. Females.

The problem ought no longer to be approached by throwing all cases of cancer together as if cancer could be treated statistically like an infective disease, as is done even to-day by many of

those who pre-judge what the future still has in store regarding the etiology of cancer, by refusing to entertain any other possibility than that of a living virus.

Instead of lumping all cases of cancer together, each organ and site must be considered separately (Fig. 3). When that is done partially and the female generative organs (Fig. 4) con-

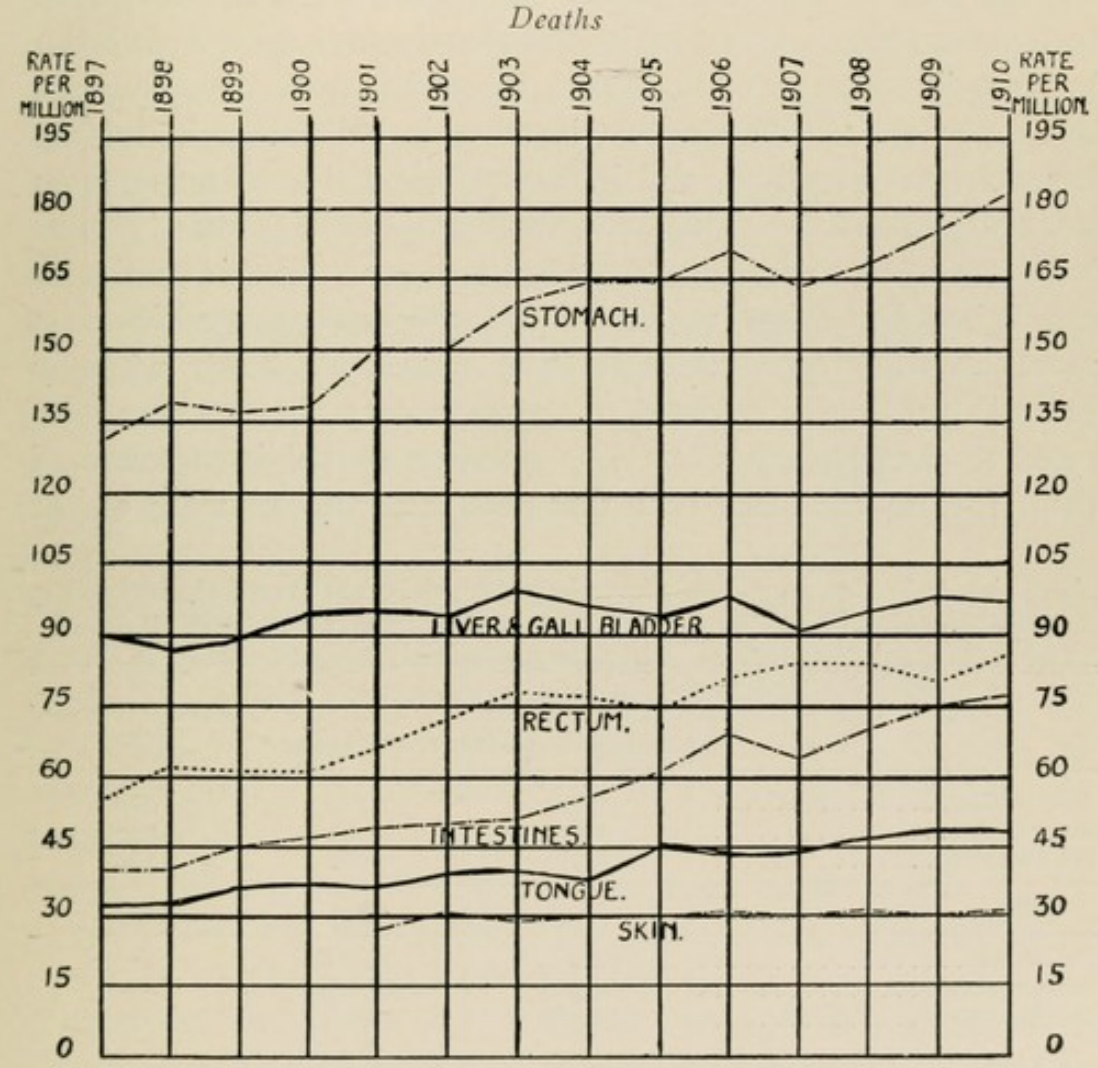

FIG. 5.—ENGLAND AND WALES.—Cancer of various parts of the body; mortality at all ages, 1897–1910. Males.

sidered apart from the rest of the body, it is at once apparent that they have not shown so great an increase as the rest of the body. For long it was pleaded that the expense would be out of all proportion to the benefit which would follow from tabulating the several organs and sites of the body separately; but the English

national statistical office and the Imperial Cancer Research Fund have at last obtained this separation, and these data are available from 1901 (really 1897) onwards for 50 different sites. The figures definitely prove how unequally the different parts of the body share in the increase in the number of deaths recorded. For some parts of the body there has been no increase at all during the past 13 years, *e. g.*, the skin, liver and gall bladder in both sexes (Figs. 4 and 5); the uterus and ovary show little or no increase in contrast to the breast, for which there is an increase of 28 per cent. The greatest increase in both sexes is for the stomach and intestines, and it cannot be considered apart from the standstill of the figures for the liver, where primary cancer is known to be so rarely observed at autopsy. In this particular case it is quite obvious we have to do with better diagnosis and a more accurate certification of the causes of death whereby growths previously referred to the secondary site are now allocated to the primary site. The question of the importance of these factors has often been discussed, and the influence of the

Analysis of the Cases of New Growths reported by the Hospital Authorities (Microscopical Examination has been made in all Cases), 1904–09, all Ages

	Malignant New Growths		Wrongly Diagnosed as Cancer
	Correctly Diagnosed	Not Diagnosed	
Accessible	5,854	567	488
Inaccessible	1,555	945	159
Intermediate	1,322	289	160
Total	8,731	1,801	757
Accessible	91.1%	8.9%	—
Inaccessible	62.3%	37.8%	—
Intermediate	82.0%	18.0%	—
Accessible	93.0%	—	7.0%
Inaccessible	90.7%	—	9.3%
Intermediate	89.2%	—	10.8%

accuracy of diagnosis may be illustrated by the results of a comparison of the clinical diagnoses with the pathological and histological findings for 13,000 cases treated in London hospitals.

The circumstances under which these diagnoses were made are much more favourable than obtain among the population in

general, and it should be noted that the increase in deaths affects mainly those internal parts of the body where diagnosis, as the above table shows, is difficult, or formerly was impossible before the introduction of autopsies, the great advances of surgery and histology. These factors account in part, if not wholly, for the greater increase in men, when all cases of cancer are considered together, for in them cancer is more often internal. They must be given due weight even if the almost equal importance of the improvement in certification of causes of death, and in the accuracy of statistics of population as a whole and of improved statistical methods is taken full account of. For some parts of the body no increase has taken place, for other parts the increase can be explained, if not wholly, at any rate, largely, by the foregoing considerations, but for other sites, *e. g.*, the tongue in man and the breast in women, the explanation is not so easy. Comparative investigations have shown how the relative anatomical distribution of cancer in the body is modified by other diseases *e. g.*, Biharziosis, or by the practice of peculiar customs by aboriginal races, and there is every justification for concluding that the adoption of these customs in America or in England would at once become responsible for a large increase of cancer in sites in which it is rare or does not occur at all. Hence the possibility of variations in the relative proportions of cases of cancer occurring in different parts of the body or in different areas even in the same country, from time to time, must be admitted. In any case it is still too soon to conclude that for all parts of the body the accuracy of diagnosis and of certification of causes of death had increased, but cancer itself had not increased for any single site or organ, although this explanation certainly holds for the mouse. In 1896 Livingood described in America two cases of carcinoma in a mouse, but twelve years ago not a single case had been recorded in England or in Germany. To-day, about 1,000 cases each have been recorded from Ehrlich's laboratory in Frankfort, and the Imperial Cancer Research Fund in London. Why? Simply because the disease has been looked for and found where previously it was unsuspected. The same remarks apply in my personal experience to

the cow, which is very liable to several forms of cancer. It may be asserted that it is quite wrong to talk about an increase of cancer in general, and to frighten the public unduly by extravagant statements based upon figures unworthy of the name of statistics. I am sorry to say this criticism applies with force to the United States where the registration of births and deaths is so imperfect and the difficulties bound up with the large floating population partly inseparable from the vast amount of immigration such that, combined, they render any comparison between the past and the present or between different States impossible. My remarks will have made it evident that the question of the increase of cancer cannot be discussed in general terms on the basis of lumping all cases together and stating them as so many *deaths per 1,000 or 100,000 of population,* no regard being taken of age and sex, which is the only method available for the United States. I am sorry to say it is possible for me to draw more reliable conclusions as to the incidence of cancer in the natives of some British colonies than in the population of New York.

In considering the real or apparent increase of cancer, it is necessary to regard the different parts of the body separately for other reasons, since it has been asserted, especially in Germany, that its most anxious aspect was that the increase affects mainly the younger ages. This is certainly not the case in England and I have not found reliable evidence that it is so in Germany. The accompanying tables show quite distinctly that in England it is the higher age-periods that are chiefly affected. This fact is not so remarkable if the relative proportions of persons dying of "old age" is compared with the relative proportion of deaths from cancer to deaths from all causes. Each amounted to 65 per cent. in the year 1909. Although the present generation looks after the aged better than in years gone by, there is yet room for great improvement which, as in the past so also in the future, will lead to deaths being transferred to an accurate cause of death, in many cases to cancer.

Up till now I have confined my remarks mainly to England but all the reservations and criticisms made in discussing the real

or apparent increase of cancer in that country apply with added force to all other countries. In Greece, Portugal, Turkey, and Russia, no statistics exist. For France, Denmark, Sweden, Roumania, and Bulgaria they are compiled only for the towns.

Death-rates per 1,000 Persons Living, 1881–1909

Countries (Arranged in Order of Crude Rates in 1901–5)	Crude Rates					Corrected Rates				
	1881–1885	1886–1890	1891–1895	1896–1900	1901–1905	1901–1905	1906	1907	1908	1909
Switzerland	1.03	1.14	1.22	1.27	1.30	1.10	1.12	1.06	1.11	—
The Netherlands	0.60	0.70	0.81	0.92	0.97	0.85	0.88	0.89	0.90	0.90
England and Wales	0.55	0.63	0.71	0.80	0.86	0.86	0.92	0.91	0.92	0.95
Scotland	0.54	0.62	0.69	0.77	0.84	0.83	0.94	0.94	0.94	—
Austria	0.44	0.50	0.59	0.69	0.74	0.69	0.73	0.72	0.72	—
Victoria	0.45	0.53	0.62	0.69	0.74	0.76	0.77	0.82	0.81	0.82
Ireland	0.38	0.43	0.49	0.58	0.69	0.56	0.64	0.62	0.62	0.65
New Zealand	0.30	0.42	0.52	0.59	0.67	0.75	0.79	0.82	0.79	0.82
South Australia	0.32	0.39	0.48	0.56	0.67	0.76	0.84	0.80	0.77	0.86
Prussia	0.34	0.41	0.50	0.57	0.65	0.64	0.69	0.72	0.73	0.74
New South Wales	0.27	0.36	0.43	0.54	0.64	0.80	0.85	0.87	0.84	0.90
Belgium	—	—	—	—	0.58[2]	0.49	0.49	0.51	0.54	—
Queensland	0.25	0.27	0.34	0.44	0.57	0.79	0.76	0.90	0.71	0.83
Tasmania	—	0.49	0.49	0.55	0.56	0.68	0.63	0.77	0.82	0.82
Italy	—	0.43[1]	0.44	0.51	0.55	0.45	0.51	0.50	0.53	0.53
Ontario, Province of	0.21	0.29	?	0.44[1]	0.52	—	—	—	—	—
Western Australia	0.33	0.41	0.31	0.31	0.45	0.74	0.98	0.83	0.86	1.09
Spain	—	—	—	—	0.44	0.38	0.41	0.41	0.44	0.44
Hungary	—	—	—	0.30[1]	0.39	0.38	0.39	0.41	0.42	0.43
Servia	—	—	0.06[1]	0.08	0.10	—	—	—	—	—

Therefore only the crudest comparison on the basis of the number of deaths per 1000 living is possible, and it is probable that this comparison as set out in the accompanying table is valueless.

In all probability the figures in this table illustrate simply the degree of the development of the statistics of the several countries and do not reveal real differences in the incidence of cancer. Read from above, downwards, they indicate the increasing worthlessness of the statistics from Switzerland, where a compulsory medical inspection of the dead obtains, to Servia where they probably have no value at all. Read from left to right, they indicate mainly the improvement in the statistics of each country. The figures for the United States have been already referred to.

Although comparisons between European countries are use-

[1] Four years.

[2] 3 years.

less, the study of cancer in widely removed peoples has had results of importance. It has been definitely proved that the idea that cancer is rare or does not occur at all in certain parts of the earth is false, *e. g.*, Egypt, India, Japan. In Japan there are 30,000 to 40,000 deaths a year, though the inhabitants are mainly rice eaters, and there is no discoverable difference between the parts of that country where fish enters more largely into the diet. In India, cancer is by no means rare either in vegetarian or other castes. Of course no conclusions as to the relative frequency of cancer is possible, but it has been ascertained that diet, climate, and race, if not of no importance at all, are of little moment in comparison with chronic irritation. Here again it is not by lumping all cases of cancer together, but by separately considering the several sites and organs, that advances have been made. Through chronically irritating certain parts of the body by practising certain exotic native customs the dwellers in widely removed parts of the earth have performed unintentional experiments of the highest value, in that they have thereby changed the anatomical distribution of cancer as it is known in the bodies of Europeans. Epithelioma of the skin of the abdomen, practically unknown in Europe, is very common in Kashmir, where the Kangri or fire-basket filled with burning charcoal is carried round the abdomen and leads to repeated burning. Carcinoma of the mouth, so rare in women although not rare in men in Europe, is as common in women in certain parts of India as in men. In China rice is eaten very hot by the men, who are served first by the women. The latter get the rice cold; they escape the carcinoma of the oesophagus so common in the men. In the regions of the Upper Nile cases of melanotic sarcoma are not uncommon on the sole of the foot and always subsequent upon the injury due to the entrance of a thorn. The fullest biological importance is given to these observations by corresponding observations on animals; for example in India, where cattle are harnessed by the right horn, epithelioma develops in consequence at the root of that horn but never at the root of the left one. In parts of England and Ireland cancer is very common in the liver of the cow, always associated with cirrhosis of that organ.

Thus comparative investigations have given a new and enhanced importance to the forms of chronic irritation—lupus-scar, burn-scar, bilharzia, etc.—long known, or new, like the X-rays. Like the older forms of irritations these newer, or hitherto neglected forms of irritation, have nothing in common, unless it be argued they permit the entrance of a ubiquitous cancer parasite.

In considering the importance of irritation in Europe and America again, it is necessary to consider the different parts of the body separately. In the case of the different parts of the intestinal canal, the curves of relative frequency cross at the stomach in both sexes; above the stomach cancer is more common in the male, below it more common in the female, both in the national statistics and in hospital statistics of England. This circumstance may not be without relation to the different habits of the two sexes, the male irritating the upper half of the canal by smoking, alcohol, gulping his food, etc., more than the female, who is more prone to the chronic irritation of constipation. Moreover, the unwillingness or inability of women to nurse children may not be unconnected with the increase in the number of deaths recorded from cancer of the breast. The increase for cancer of the tongue in men and the stomach and intestines in both sexes, therefore, should, perhaps, not be dismissed as due merely to improved diagnosis and certification of the causes of death.

The importance of considering different sites apart can also be argued on a comparative basis. In surveying the incidence of cancer in the vertebrate kingdom, one has been struck by the fact that certain forms of cancer appear to preponderate in different classes. It is, of course, obvious that the incidence of cancer in representatives of the different zoological classes must differ, since, *e. g.*, structures peculiar to mammals are absent in other vertebrates. But if we consider the mammalia themselves, it appears probable that some species are very liable to forms of cancer from which others, even nearly allied, are relatively or altogether exempt, as illustrated, *e. g.*, by the variations in the frequency with which cancer of the uterus or mamma occurs. Cancer of the breast, so common in the human female, is also

common in the mouse and dog, but practically unknown in the cow which, however, suffers quite frequently from primary growths of the liver and adrenal. These tendencies are so constant that it is difficult to escape the conclusion that they depend on innate characters which are hereditarily transmissible, and there can be no doubt as to their etiological importance, although we cannot yet penetrate to their meaning.

Even in the same species we meet with similar idiosyncrasies, *e. g.*, in the greater liability of grey than of other horses to melanotic sarcoma. It may, of course, be argued that these peculiarities of incidence of the disease are determined by peculiar environment or by the use to which the organs are put in different species, although this would hardly hold for grey as contrasted with other horses, the disease in question affecting only the pigment-cells of the skin. If we compare the tame albino mouse with the wild grey mouse, the incidence of cancer is parallel in them, although the two varieties live under very divergent conditions; therefore the liability of the mouse to carcinoma of the mamma appears to be due to an innate tendency.

When we compare the large natural groups of vertebrates, or even the species of the mammalia, the grounds on which we may assume that differences in the incidence of cancer are innate and hereditarily transmitted appear safe. But when we come to compare the differences in the incidence of cancer in the individuals of a species we are not on such certain ground.

I must now preface what I have to say about the experimental study of the biology of the tumour cell by a brief account of investigations in which the statistical and experimental methods are combined, inasmuch as the latter method is employed to elucidate a problem statistics have precised.

In the first place it was necessary to ascertain if the reason why cancer occurred with greater frequency in the old than in the young was due to a constitutional change suitable for the growth of the cancer cells. It was found at once that young animals were more suitable for inoculation and for growth. It was therefore made evident that the origin of cancer was distinct from its continued growth and the influence of senescence was bound up

with the origin and not a constitutional change favourable to continued growth of the tumour once it had developed. This result as to suitability for growth had to be followed up further, but in order to do so a stock of mice liable to cancer had to be made available.

The influence of heredity is undetermined and perhaps not capable of settlement in men owing to the length of life. For upwards of eight years atempts at breeding mice from cancerous parents have been made. Until 1909 no result was obtained showing that cancer had thereby become a more frequent occur-

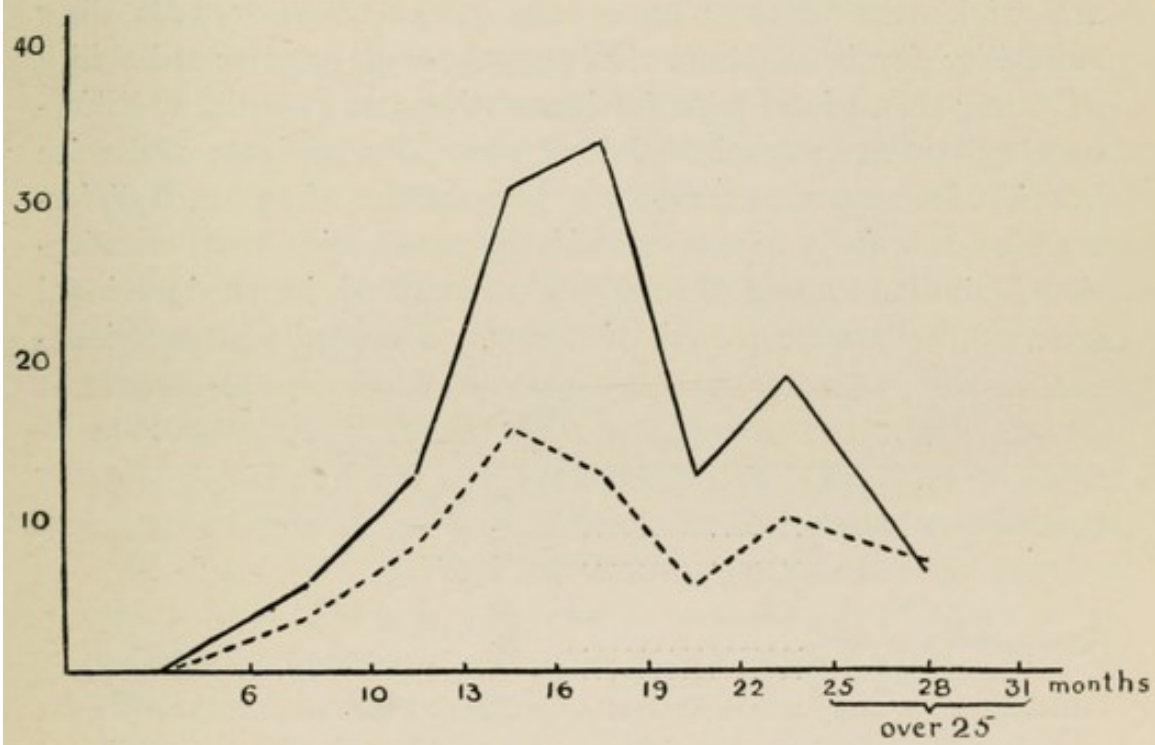

FIG. 6.—Percentage of deaths from mammary carcinoma to deaths from all causes at successive 3-monthly age-periods in female mice of recently cancerous ancestry (mother, grandmothers) ———, compared with the same ratio in female mice having more remote cancerous ancestry (mother and grandmothers non-cancerous) -- -- -- -- --.

rence. Many generations of mice have now been under observation in whom upwards of 800 tumours have developed naturally. The accompanying curve giving the results of Murray's later observations show how much more frequent cancer of the mamma is in mice whose mothers or grandmothers or all three

suffered from cancer. It must be noted that this result has only been obtained by an amount of inbreeding and of concentration of the hereditary factor which occurs very rarely, if at all, in the human subject. In effect the observations tend to show that although there is an hereditary factor, in all probability it is not of sufficient moment to cause alarm as regards human beings. The possession of a stock of mice with this higher susceptibility permitted another experimental method to be resorted to, in order to discover any constitutional peculiarities of the animals and the relation obtaining between the tumour and the animal in which it arose. Normal and cancerous mice of different ages and of known ancestry have been compared as regards their suitability for inoculation. In regard to the greater suitability of young than of old mice for inoculation and growth, no difference exists between mice of long cancerous pedigree and mice devoid of a cancerous ancestry. The absence of any such difference led to efforts to ascertain if cancerous mice were constitutional similar among themselves or behaved in an individual manner towards the growth of cancer. The method was to inoc-

	Mice with Spontaneous Cancer			Normal Mice
	A	B		
Spontaneous Tumour A	+	−		− 0/35
" " B	−	+		+ 3/35
	C	D	E	
Spontaneous Tumour C	+	−		− }
" " D	−	+		− } 0/1000
" " E	−	−	+	+ 4/26

ulate the spontaneous tumours into other mice having spontaneous tumours, and also to re-implant them into the mice in which they had arisen. The results of Haaland's observations given in the accompanying table show how great is the difference between re-inoculating a tumour into its own mouse and inoculating it in any other mouse, whether normal or suffering naturally from a growth of its own. Re-inoculation with an animal's own tumour succeeds in 100 per cent. if there be no untoward accident. On the other hand, success is as rare in other cancerous mice as it is in normal animals. Thus it was proved that cancer

does not grow because of a constitution or a soil suitable for the growth of cancer, in general. A lowering of the affinity of the body cells as a whole for food-stuffs with retention of a higher avidity by the tumour cells would not, for example, explain cancer. It was made evident that the origin and growth of cancer involved problems individual to each animal, and—in the absence of any evidence of a constitutional change favourable to the growth of cancer—it appears possible that the hereditary influence is rather one of the tissue affected than any change in the body as a whole. This conclusion as to individuality has been borne out by other observations. Normal mice, young and old, have been housed in the same room for the length of life, together with mice highly susceptible to and constantly developing cancer; but no excess of cases occurred in the former. They were no more liable to cancer than mice kept free from all such outside influence. The same negative result has also been obtained where, during many years, as many as 10,000 to 20,000 mice inoculated with cancer have been kept in one room together with normal animals. Tumours did not develop with any greater frequency than in animals not so exposed. These results agree with those for men, since it cannot be shown that the density of population has any influence on the frequency of cancer in contrast with its marked influence in the case of tuberculosis.

The bearing of all this statistical study on etiology is that it gives no sort of indication that a problem of infection is involved, although the importance of chronic irritation and of an inherited and possibly a tissue susceptibility is clearly brought out.

The irritants having nothing in common, it seemed rational for this and other reasons to seek for the common factor in properties of the tumour cells themselves, and to follow up the unintentional experiments of native races, by carefully observing the behaviour of tumour cells during years of prolonged proliferation, more especially because at the very beginning of our experiments we noted such marked variations occurring from time to time in tumors of the same strain, that a person ignorant of its history would certainly have held they were really distinct growths.

Lecture II.

Experimental Study of Tumor Cells

Up to the present, tumours of mammals when transplanted into other individuals have grown progressively only in other animals of the same species. An inoculation of a tumour from another species does not alter the suitability of an animal for the subsequent transplantation of a tumour of its own species. The claim has been made that resistance could be produced in this latter way; but our very extensive observations show that the constant result is as stated, whereas the occasional and apparent protection obtained after inoculation of strange tumour is explicable by accidental circumstances. If the animals are ill from any cause, *e. g.*, from a too large inoculation dose, sepsis, enteritis, etc., they are rendered less suitable for transplantation, and an appearance of resistance is produced. This point is of importance because the apparent protection after inoculation of a tumour of a strange species has been used as evidence that the tumours of different species, especially the sarcomata, have something in common in the nature of a parasitic etiology. As a matter of fact the inoculation of mice with transplantable rabbit or rat sarcoma has no effect upon a later inoculation of mouse sarcoma. Thus, the specificity of cancer is proved in two ways: by absence of power to grow progressively in a strange species and by failure of a strange tumour to induce resistance to homologous inoculation. The specific character of tumours is, however, brought out even more clearly by the induction of resistance by means of the normal tissues of the same species, but not of a strange species. Even in the same species biological differences between tumours can be detected by these methods. If a tumour be inoculated which takes in 100 per cent. and all the resulting tumours soon undergo spontaneous healing, the animals will then be found to be completely protected against a re-inoculation of

the same tumour. Against other tumour strains there may be complete or incomplete protection, or, indeed, there may be no protection at all. In this connection there appears to be some difference between carcinoma and sarcoma, and although the subject requires further investigation it seems that sarcoma protects better against carcinoma than the latter does against sarcoma. Thus, there is a degree of immunity which is common to all tumours of a species, a pan-immunity in Ehrlich's sense, and degrees of immunity which are specific. The pan-immunity de-

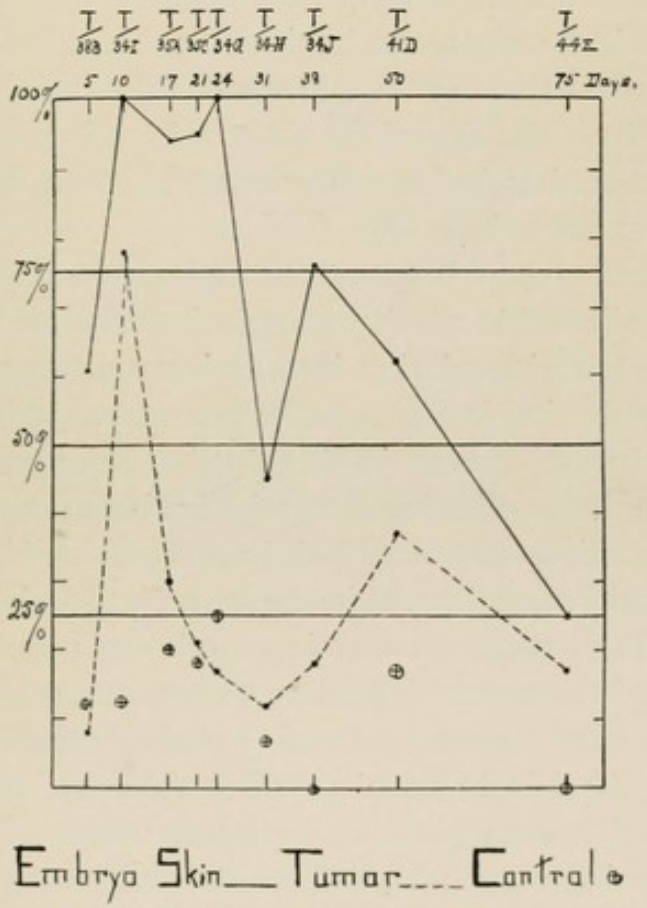

FIG. 7.[1] Similarity of resistance produced by tumour and by normal tissue respectively.

pends on the properties of the tumours as tissues of the species; the specific differences in the tumours will be considered later. The high degree of protection produced by normal tissue is most remarkable, as the accompanying curves from Woglom's experiments show. The two curves run parallel and the comparison

[1] Reprinted by courtesy of the *Journal of Experimental Medicine*.

established between tumour and normal tissues shows that the resistance induced by tumour is not due to any foreign agency. When normal tissue is inoculated, necrotic tissue and other irregularities inseparable from tumour are avoided; therefore, too much weight must not be laid upon the fact that normal tissue induces a higher degree of resistance than does tumour tissue. Nevertheless, this difference may have some etiological significance and will be referred to again.

In order to induce resistance the normal and tumour cells must be alive. If their vitality be destroyed in any way, *e. g.*, by heat, chemical means, mechanical crushing, or radium, the power to induce resistance is entirely lost. Unable to separate this property from the life of the cells, we are in a position similar to that obtaining before the ferment action of yeast was separated from the living cells.

The resistant change is spread throughout the body, and statements to the effect that a subcutaneous inoculation will not protect against a later inoculation into an internal organ are erroneous. The protection is just as effective there, and, indeed, can be shown to be active even in the blood. If tumour emboli be induced in the lungs of mice immunised with normal or tumour tissue, the emboli do not develop into tumours as in normal animals, but remain confined within the vessel walls and degenerate. It is evident that complete protection can be conferred against the introduction of the cancer cell from without, so that were cancer spread in this way or communicated from individual to individual as has been alleged in so-called *cancer à deux*, we should already be able to confer exemption on the community.

The foregoing results have reference only to testing animals by an inoculation. Once a tumour has established itself the resistance has much less effect, except in the case of tumours which induce resistance to their own growth and in consequence undergo spontaneous healing. An animal's own tissues do not induce any resistance against tumour inoculation. Animals already bearing transplanted tumours can be immunised against a second inoculation, so, also, mice with spontaneous tumours can be protected against the inoculation of a transplantable tumour; but in the

latter case the resistance is without any effect upon an inoculation of an animal with its own spontaneous tumour. The progress of spontaneous tumours and the formation of metastases is in no way affected by any of these methods. Mice which have been kept immunised for months will develop spontaneous tumours of their own, which fact also speaks for the endogenous origin of cancer. These facts discredit all claims to cure cancer by means of autolytic products, vaccines, or immune sera. The importance of the resistance that can be induced against inoculation is purely biological, enabling us to obtain information on some hitherto hidden qualities of the tumour cell and its relation to the organism, and leading to the inevitable conclusion that every case of cancer is a problem individual to the person in whom it develops. They have no therapeutic value as yet and it is not apparent if they ever will have any. Furthermore, they throw no light on the great frequency of cancer.

Other observations to which I have already referred have explained the relative frequency, in different human races, of certain forms of cancer associated with chronic irritation. Similar conditions were also noted for animals and the fact also alluded to that cancer has special predilections for certain mammalian organs which are exempted in other species.

I pass now to consider the results of the prolonged propagation of tumours of the mouse, which is peculiarly liable to cancer of the mamma. This is a biological problem of as much importance as the great liability of the human female to cancer of the breast. In the case of the mouse, Haaland has shown how common is chronic inflammation in the mamma of old females and has pointed out one cause, viz., the presence of nematodes, though it does not follow that this is the only cause. The chronic inflammation is associated with hypertrophic nodules and adenomatous and cancerous changes in the epithelium in all combinations. A similar combination occurs in the liver of cows, where cirrhosis, hypertrophic nodules, adenoma, and carcinoma—with extensive metastases in the lungs and lymph glands—are frequently combined. The cirrhosis is here associated with the presence of liver-flukes in the bile ducts, but it is by no means certain that the

cirrhosis is not due to some chemical substance absorbed from the food. Thus, the more comparative the study of chronic irritation becomes, the more it increases in importance as a mediate or indirect cause of certain forms of cancer. It is almost certain that an irritant effective in one species of mammal will not be an effective *i. e.*, indirect, etiological factor in another species. The forms of irritation are manifold; they have nothing in common beyond their causing cell injury and their induction of cell proliferation. When tumours are transplanted the cell proliferation is simply prolonged artificially, and in reality by again causing cellular trauma we are continuing the experiment which had occurred naturally. This prolonged propagation of tumours has been criticised as of no etiological value, but I shall show you how greatly it has added to knowledge, and that by observing the behaviour of tumour cells over a prolonged period certain inferences may be drawn as to how the cancer cells were likely to behave before they were placed under experimental conditions. The longing expressed by Goodhart in 1875: "What a subject for Darwin would be the cells of a cancer if only they were tangible; how the immortal pigeon would be completely eclipsed, while the hungry pathologist would be filled with food, if we could observe the variation of tumours under judicious cultivation!" has now been gratified, if cancer has not yet found its Darwin.

For more than ten years the behaviour of a large number of transplantable tumour strains has been carefully noted. The observations fall mainly into two groups, those relating to morphology and those bearing on the phenomena of growth. It is impossible to consider here all the factors concerned in the first transference of a spontaneous tumour to normal animals. It is a true transplantation, the daughter tumours developing from the tumour cells, whilst the host supplies the connective tissue and vascular scaffolding. A certain selection is effected of those cells adapting themselves to the strange conditions or able to live under them. The soil acts, as it were, as a sieve allowing certain cells to pass, selecting only some that are capable of growth. At the next transplantation these have increased in number, and

by the third or fourth *passage* the percentage of takes reaches a level which has remained constant for years for the majority of our tumours, when grown in as many parallel sister strains as possible. Most of the tumour strains show as yet unexplained and apparently periodic fluctuations from time to time. There are, however, some remarkable exceptions to constant behaviour and to them special reference will be made.

When a tumour is transplanted it undergoes entire histological disorganisation. This process has been repeated over and over again every seven or ten days, or after longer intervals, for years. Assuming that the only common factor for all the irritants associated with cancer is their power to induce proliferation, the process is as analogous as is possible to the chronic proliferation which precedes the development of cancer, always bearing in mind that it is the ready made tumour or cancer cell which is being studied. Notwithstanding the fact that we are not producing the cancer cell at will, but are merely studying its behaviour—since it is clearly demonstrated that the cancer cell is a genealogical descendant of a normal cell—we are justified in assuming that the propagated cancer cell will behave similarly to its genealogical *ascendants* in its host of origin provided, of course, that we largely neglect the possible influence of strange environment.

After the disorganisation caused by transplantation, it is necessary to give time for a tumour to resume its normal habits. Therefore, it is advisable to study not merely the material preserved at the time of each transplantation, but also tumours that have grown for some time. It is then found that the characteristic histological structure is reproduced as a rule, it may be very rapidly, or it may be only after prolonged growth. This characteristic differentiation occurs in spite of the fact that the connective tissue and vascular scaffolding has to be reproduced anew by each fresh host, taking place with equal regularity in adenoma, cystic papilliferous carcinoma, and solid carcinoma of the mamma, as well as in squamous-celled carcinoma and in adenoma of the sebaceous and preputial glands. The latter, notwithstanding years of propagation, still reproduces a structure which cannot be distinguished under the microscope from the normal

preputial gland. The conclusion clearly follows that tumours which histologically are "benign" can be propagated for the same length of time as those which are devoid of all differentiation and are in current terminology histologically "malignant." Experiment therefore supports clinical experience in its inability to establish a sharp division between benign tumours—for which a parasitic etiology is not assumed—and the malignant new growths for which a parasitic etiology is asserted to be essential.

Other more subtle features revealed by microscopical technique may be retained unaltered, *e. g.*, tumours which form glycogen in large droplets have continued to do so for years, from the spontaneous tumour onwards. A tumour strain which caused a sarcomatous transformation of the connective tissue scaffolding supplied by the new hosts has continued for six years to effect this change in every mouse in which it has grown for 60 days.

In 1905, attention was drawn to the fact that the propagated tumours derived from a single parenchyma, viz. the mammary epithelium, varied so much in microscopical appearances that a person ignorant of their life-history would declare them to be of distinct primary origin. This early observation led to the extensive propagation of a large number of tumour-strains of separate primary origin, as many as 86 strains being kept in propagation at one time, many of them in several parallel sister strains. The net result is that the histological differences present at the outset of propagation of tumours arising from the same parenchyma, remain in many cases constant, and are, therefore, to be regarded as true variations of relative constancy. The further conclusion may be drawn that the change which occurs in the transformation from normal to the cancer cell deeply affects the cell mechanism, and not only in one way, but in several ways.

Although the constancy with which strains maintain their histological features is most noteworthy the exceptions to this general rule are perhaps of even greater biological significance. Two squamous celled carcinomata have grown for years and have always shown complete differentiation; but another one behaved in this way only up to the ninth transplantation and

has grown for years without any reappearance of keratinisation. A fourth tumour of the same kind has also behaved in the latter way, and some adenomatous tumours have likewise lost all evidence of acinous differentiation. There are adenomatous tumours which have exhibited a most remarkable histological change; after transplantation there is the usual undifferentiated cell mass, but areas of spindle cells appear later, indistinguishable histologically from spindle celled sarcoma, which later differentiate again into typical acini and reproduce the picture of the mother tumour. This spindle celled appearance may also become constant, and only in the very oldest tumours may there be found evidence of the tendency to acinous differentiation. Similar morphological changes have also been observed among the propagable sarcomata. An osteo-chondro-sarcoma has been grown in two parallel strains. One shows a great tendency to necrosis and is soft to the touch, the other feels hard and forms much collagen. Both strains have lost all tendency to form either cartilage or bone, and cannot be identified with the mother tumour except from their life histories. As a last example an adeno-carcinoma which has been grown in 18 parallel sister strains may be referred to. It illustrates alike the constancy and the variability of the histological structure and other properties of the epithelium. For three years some of the strains of this tumour caused irregularly sarcomatous transformation in the stroma, and the transformation was to spindle-, round-, and polymorphous-celled sarcoma. Other sister strains possessed no such property but have grown as pure adeno-carcinoma or as pure solid carcinoma. Now, after several years, all the strains have lost the power to produce sarcoma. One of these strains, although remaining a pure epithelial tumour, grows with a spindle-celled parenchyma exhibiting slight tendency to acinous formation in very old tumours.

From these observations it follows that the morphological variability of tumour cells is as completely demonstrated as is the constancy with which they may retain their histological features.

The phenomena of growth are equally interesting. They have been carefully noted during ten years for some 80 tumour

strains. At one end of this series there is a strain growing in every animal with great rapidity and forming metastases in over 80 per cent. of the mice. At the other end there are tumours taking also in 100 per cent. but also completely healing in each animal. There are other strains which take in a very low percentage and grow very slowly. The intermediate tumours represent the utmost variety of combinations of these features. Tumours which take in 100 per cent. but which all disappear after transitory growth resemble normal tissue in this respect, although, of course, normal tissue has not been found capable of unlimited propagation. In order to have some stand-

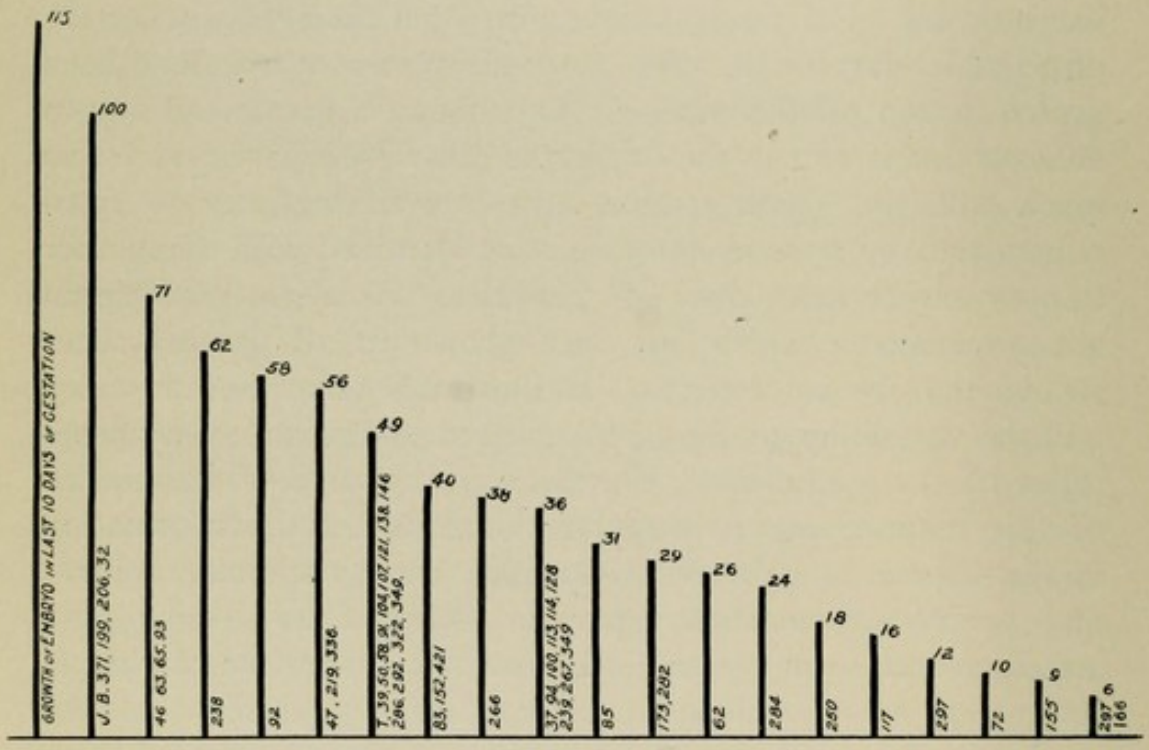

FIG. 8. Diagrammatic comparison of rate of growth of various tumor-strains on the basis of the number of days required to produce 1 grm. of tissue from a measured dose (0.2–0.3 grm.) inoculated. The rate of growth of embryonic tissue is also indicated on the basis that the mouse embryo weighs 0.02–0.03 grm. at the 11th day of gestation and at birth 1–1.5 grm.

ard for comparing the rates of growth of these tumours they have been contrasted with the rate of growth of the mouse embryo as shown in the accompanying diagram (Fig. 8). Ten days before birth the mouse embryo weighs 0.025 grm. and at birth about

1 grm. For years all tumour strains have been inoculated in doses of 0.025 and the developing tumours weighed at ten days. This method, of course, does not permit of exact comparisons, but it permits of a rough comparison, and brings out the fact that the tumours show all rates of growth. Some may be said to equal the rate of growth of embryonic tissue, others fall far short of it. This is one more experimental proof that the progressive growth of cancer cannot be explained by analogy with embryonic growth.

As regards the relation between structure and rate of growth, it can be stated that as a general rule the most rapidly growing tumours exhibit least evidence of differentiation. There are exceptions *e. g.,* when a tumour devoid of all differentiation is also one of the most slowly growing, or when a well developed acinous structure is associated with rapid growth. Some strains showing full differentiation, *e. g.,* squamous-celled carcinoma and adenoma of the sebaceous glands grow extremely slowly.

As regards dissemination, the frequency of lung metastases varies from strain to strain. In general, they are more frequent for rapidly growing strains, the most rapidly growing of our carcinomata, *viz.,* strain 63, giving them in as many as 80 to 95 per cent. of the mice inoculated, provided they live long enough afterwards.

The comparison of rates of growth given above for different tumours extends over many years and permits of the conclusion that, for most, the type of growth is constant, once the earlier *passages* have been got over. The features of growth may be as persistent during years as the retention of histological structure. It is not the general rule for a gradual increase in the rate of growth to take place from the slowest to the most rapid, and in several instances the deliberate attempt to attain this has not been successful. It seems therefore that the type of growth is in most cases a primary quality of the tumour cells, imprinted on them at the time of the cancerous transformation; like the morphological features it exhibits a number of varieties of relative constancy. There are, however, important exceptions where a remarkable change has taken place. In some cases it may

be only that where tumours were liable to spontaneous absorption, this event is postponed for a longer interval after transplantation. There may be a higher percentage of takes. There may be apparently more rapid growth. The most startling example of such changes is seen in strain 63. Several sister strains were grown from the original material and two are still retained in propagation. The one still reproduces to-day the behaviour characteristics of the earliest *passages,* when the percentage of takes and the rate of growth were moderate, while a large number of tumours underwent spontaneous healing. The other parallel strain grows progressively in every mouse with great rapidity, and never shows spontaneous healing. If the mice live long enough most of them show metastases in the lungs. These experiments show that just as it may be impossible to recognize the relationship of daughter tumours to the original material owing to variation in the histological structure, so also the variation in powers of growth may be equally great. The conclusion is thus arrived at that during the prolonged propagation which is ever being interrupted by the trauma of a fresh transplantation, what are really *new* tumours have arisen. The power of progressive growth and of dissemination may be so completely acquired that the tumour-strain behaves in normal animals like a spontaneous tumour in its host of origin. In other words, the possible influence of a strange environment can be left out of account in this instance. It appears therefore that the study of propagated tumours has thrown a little fresh light on why some forms of cancer may arise in association with chronic irritation, although it has not given an explanation of the differences in the behaviour of normal and tumour tissue. The following observations have however also taken us a step in this direction.

It has been pointed out that whereas some tumours grow progressively in all animals and form metastases, others only grow for a time and then disappear, and also that all intermediate stages have been observed. The possession of such a comparative series of tumour-strains has made it possible to ascertain one reason for the difference between the two chief groups into which

transplantable tumours may be divided. The experimental method is to inoculate a tumour-strain and then determine the suitability of the animal for a secondary inoculation. The results were at first contradictory, but the extremely careful investigations of Russell have led to the tumour-strains being placed into two chief groups corresponding with those that grow progressively in every animal and those which after transitory growth undergo spontaneous healing in every animal. It has been clearly demonstrated, as the accompanying lantern slides show, that in the first group a re-inoculation is always successful; in the second it always fails. In other words, the first group does not induce any resistance to a secondary inoculation, and the second group always does so. The conclusion drawn is that the first group does not induce resistance to its own growth, whereas the second group does so by virtue of a resistance which it induces and which develops concomitantly with the growth of tumours after transplantation. In the intermediate groups of tumours the individual reaction of the animals plays a more prominent part in permitting progressive growth in one instance, and in another, in leading to spontaneous healing. Attention has already been drawn to the evidence that normal tissue induces a higher degree of resistance than does spontaneous tumour tissue and this evidence may be correlated with the following phenomena. As has been shown, normal tissue only grows transitorily after transplantation and induces resistance to subsequent tumour inoculation. Although it is difficult of clear demonstration, the analogy with the spontaneous healing of some tumour strains makes it almost evident that the induction of this resistance is responsible for the transitory growth of normal tissue. It is certain that the induction of this concomitant resistance or immunity determines the occurrence and frequency of the spontaneous healing of certain tumour strains, and the question arises what happens when from tumour material capable of only transitory growth, there are grown two parallel strains, one retaining this peculiarity and another capable of progressive growth and of metastasis-formation. Careful investigation demonstrates that the power of progressive growth of such sister

strains is acquired because they have lost the power to produce resistance to their own growth. For the other alternative, that the tumour cells might acquire a power to overcome the resistance when induced, there is as yet no evidence whatsoever.

It would be easy to enter into a hypothetical discussion of the possible bearings of these facts ascertained for transplanted tumour cells, upon the behaviour of tumour cells in their hosts of origin. It seems, however, at this stage sufficient simply to raise the question of whether or not they throw new light upon the regulation and control of normal growth and the unregulated and limitless growth of cancer.

Before concluding it is necessary to refer to the phenomenon of natural healing in spontaneous tumours, because statements calculated to give an entirely false impression have been widely disseminated. For about 700, or when multiple tumours are considered, about 1000 spontaneous tumours, very careful observation of their clinical course has been kept for weeks and months. Healing has not occurred in 1 per cent., as contrasted with transplanted tumours, for which it can be obtained in any desired frequency by simply choosing the suitable tumour-strains. The processes for spontaneous and transplanted tumours may be followed histologically and they exhibit close parallels. There is some primary change in the tumour cells, which although not yet understood, appears to be an essential preliminary. Ultimately the dead tumour cells are taken up by phagocytes, and the formation of a typical scar tissue completes the process. For transplanted tumours the process can be followed in detail by examining the site of inoculation in animals which have been made highly resistant by the inoculation of tumour or normal tissue, and instituting comparisons with the corresponding periods after inoculation into normal animals. There are then distinct differences observable in the two sets of animals. In both there is a reaction of the connective and vascular tissues of the host. Whilst the normal animal reacts in such a way that the implanted piece of tumour again acquires the specific stroma and vessels which reproduce the original structure of the tumour, the immune animal does not so react. In the latter case the

specific reaction which supplies the characteristic connective tissue and vascular scaffolding is not elicited. The tumour cells are not at once killed, indeed they may be observed undergoing mitotic division; but ultimately they die and suffer the consequences of the formation of scar tissue. The explanation is to be sought in a paralysis of the chemotactic influences which proceed from the tumour cells.

For the numerous observations which have now been outlined, it cannot be claimed that they afford anything approaching to an elucidation of the problem of cancer. It is only certain that they have thrown new light on some old problems and at the same time that they have revealed others hitherto unsuspected. An interesting feature is the relations brought out between connective tissue and epithelium, *e. g.*, in the experimental induction of sarcoma by certain carcinomata, the relation between chronic inflammation of the mamma of mice and carcinoma, cirrhosis of the liver and carcinoma, and the power of the transplanted tumour cell to mould the connective tissue and vascular scaffolding to the features characteristic of the original tumour. In sharp contrast is the failure of the cancer cell to dominate the connective tissue in the immunised animal or where spontaneous healing is taking place. In every one of the experimental instances of the relations obtaining between the cancer cell and the connective tissues, it is the influence proceeding from the cancer cell itself or the paralysis of this influence which plays the predominant part. The same part seems to be played in the natural healing of spontaneous tumours, since in the same animal one tumour may go on growing while another is healing. We are here face to face with as yet unsolved problems the solution of which, without doubt, will carry us further. In the meantime we have not succeeded in defining what is responsible for the change, and it is therefore most surprising that attempts, which to my mind appear empirical, are being made to cure animals of transplanted tumours. The claims of Wassermann to have cured mice of transplanted tumours by means of eosin-selenium compounds and also those of Neuberg and Caspari to have attained the same end by augmenting what is described as the normal

autolytic process, while interesting and suggestive, have no rational basis in anything I have related to you. I would not be misunderstood as being a person hostile to what in the terminology of Ehrlich is known as chemotherapy applied to cancer, for I have the honour to be one of Ehrlich's pupils, and at the same time also to be a pupil of Fraser who with Crum Brown was the first to describe the relation between chemical constitution and physiological action. My position is simply this, that we have not yet defined where and how an interference with the pernicious physiological activities of the cancer cell can be rationally applied. Until this knowledge is attained all claims to cure cancer must remain empirical, although it does not follow that the search for empirical remedies is to be discouraged in such persons as care to undertake it. For my part, I counsel the continuation of rational experiment into the mysteries of the nature of cancer, and I trust that the facts I have set out as the result of the ten years of investigation by my colleagues and myself have convinced you that the next ten years of experiment will reveal yet other new facts to those experimentalists who have the patience to continue these laborious enquiries.

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