Notes on Cancer

The mortality from cancer appears to be slowly increasing. The crude death-rate in 1936 was 1,625 for both sexes per million living, the rate for males being 1,612 per million and for females 1,636. The rate in the period 1901-05 was 867, and in 1937, 1633; the rate now is twice that at the beginning of this period.

Nearly half the cancer deaths (48 per cent) occur in persons under 65 years of age. During the working period of life, from 15 to 65 years of age, 17 per cent of all the deaths which occur are attributable to cancer.

Most investigators are now agreed that the recorded increase in mortality does not necessarily mean augmentation of general constitutional factors. The rising rates, however, do increase the seriousness of the administrative problem of provision of adequate means for diagnosis and treatment.

In the text volume of the Registrar-General’s Review a table of standardized mortality rates for individual organs appears for the most important sites for each sex. From this table it appears that in accessible organs, such as the lips, tongue, jaw, uterus and skin, while the rates have fallen considerably between the earliest and latest periods, they have remained practically stationary, with a tendency to fall, in the last five years. In these accessible sites in which increasing accuracy of diagnosis has played only a small part, the falls are probably due to a combination of diminished frequency and the effect of treatment. Another group consisting of the stomach, intestine, rectum, lung, pancreas and prostate shows a marked rise over the longer period and a tendency to rise over the shorter period. On the rates for such organs treatment can have little effect and the rises are due to increased incidence combined with more accurate diagnosis, or both. Experience suggests that improved diagnosis is the more important. This receives support from the fact that in an intermediately placed group, the pharynx and oesophagus, where the influence of diagnostic and therapeutic changes is small, the changes in the rates are small suggesting that changes in incidence are also small.

Investigation into the cause of cancer through laboratory research continues with increasing vigour, and details of the various experiments are given in the Report of the British Empire Cancer Campaign, and in the report by Dr. Gye of the work carried out by means of the Imperial Cancer Research Fund.

Research work is also being carried on at the Royal Cancer Hospital, the Middlesex Hospital, cancer research laboratories and other large
hospitals in London. In the provinces, there are centres at Sheffield, Leeds, Newcastle, Birmingham and Manchester. The Medical Research Council's investigations extend to research in all medical problems including cancer.

In less than a lifetime both knowledge and treatment in regard to tumours have improved out of recognition. It is only within the last few years that operations for cancer have been based on a precise knowledge of the spread of the disease. The causes of cancer yet remain obscure; but there is no doubt about certain of the causes, viz. the synthetic preparations. The study of growth stimulating and growth inhibiting substances seems likely to be a profitable field of research.

The major part of research has been directed fairly closely into two main channels: those connected with carcinogenic substances, and those initiated by the discovery of virus tumours in fowls.

In 1935 Dr. M. des Ligueris of South Africa reported that he had succeeded in inducing a malignant transformation in tissue cultures of normal chicken fibroblasts by adding a small amount of dibenzanthracene to the culture medium in which the cells were growing. Inoculation of chickens with these cultures resulted in the production of rapidly growing sarcomata from which after a number of serial transplantations a filtrable virus could be extracted. Immunological experiments with the des Ligueris sarcoma have shown that it is closely related to Rous sarcoma No. 1, and perhaps more closely to the Fujinami tumour, being like it communicable to ducks.

It has been found that if the Rous sarcoma agent is present in the body of a fowl it may pass to a chemically-induced tumour present at the same time. It has further been found that the Rous virus will pass not only from the Rous tumour to other tumours of chemically-induced type but also to the normal tissues. Extracts of many organs and tissues of fowls bearing the Rous sarcoma will produce new tumours when injected into fowls. These organs and tissues are free from sarcomatous growths, although rich in the sarcoma-producing agent.

Recent syntheses of derivatives of 1:2 benzanthracene has led to an increase in our knowledge of the types of substitution which lead to cancer-producing activity in the benzanthracene hydrocarbons. In this connexion it is of interest that 9:10 dimethyl-1:2 benzanthracene has proved to be the most rapidly acting chemical cancer-producing agent yet found as tested by capacity to produce cancer of the skin.

Many hydrocarbons known to be carcinogenic have been found to exert an inhibitory effect on cellular proliferation. It is suggested that these substances act by producing a prolonged retardation in the growth of the affected normal cells which eventually react by the production of a new cell type with permanently lowered differentiation and a correspondingly
increased fission rate. In this view the cancer cell is supposed to be a
somatic variant developing in adaptation to protracted inhibition. The
view is supported by the relative resistance of chemically-induced tumours
to the inhibitory action of the carcinogenic hydrocarbons.

Work on the action of carcinogenic compounds on the growth rate of
spontaneous tumours of the mouse has confirmed the inhibiting effect of
parenteral administration $1:2:5:6$—dibenzanthracene, which has been
accompanied by partial regression in some 18 per cent of cases.

In the induction of epitheliomata, carcinogenic substances act not only
on the epithelium which ultimately supplies the tumour cells, but also on
the deeper tissues. The ultimate effect may be due to impairment of the
nutrition of the epithelial cells.

Extracts of certain tissues exert an accelerating effect on the growth of
chick fibroblasts \textit{in vitro}, whereas extracts of other organs have no such
action. Extracts of brain are more active in this respect than extracts of
embryonic or other tissues. The growth-promoting power evidently does
not depend on the rate of growth of the tissues from which the extract
is obtained, but the tissues which are most active possess the most active
powers of anaerobic glycolysis. The energy for growth seems to be in
some way connected with the change from glucose to lactic acid.

It has been disputed whether cancer spreads within lymphatic channels
as small emboli or by permeation. This question seems to have been
settled by injections carried out with Thorotrast injection methods. These
show that cancer spreads by means of minute emboli which are carried
along the lymphatic channels and are arrested in the lymphatic glands.
Thorotrast injections have shown the vessels to be patent, and certainly
not permeated with cancer cells.

An investigation of the relationship between histological appearance
and prognosis has shown that in the case of mammary cancer the presence
or absence of axillary metastasis is the most important single factor in
prognosis. Histological grading is of value when combined with the
results of examination of the lymphatic glands. In a series of 172 patients
only 19 per cent survived for ten years, but of the patients with Grade I
tumours and no axillary metastases 57 per cent survived for this period.
Age has little effect on the prognosis.

Reporting on the work of the Imperial Cancer Research Fund, Dr.
Gye points out that the work in the laboratory at Mill Hill confirms
observations made elsewhere.

In the Section on Carcinogenesis there is a renewed warning of the
dangers of using Thorotrast in radiography. The substance appears to
remain in the body indefinitely, and Dr. Foulds has produced both
sarcoma and carcinoma at the site of its injection into guinea-pigs.
Though no cancers have yet appeared in human beings, it is considered premature to assume that Thorotrast is harmless, especially as bone tumours appear in workers who handle luminous paints.

Tar and carcinogenic hydrocarbons evoke squamous epithelioma when applied to the skin, or sarcoma when injected beneath it. The carcinoma produced by Dr. Foulds in the guinea-pig is apparently the first example of a glandular cancer produced by the local action of a carcinogenic agent.

Rous showed that if a rabbit's ear was painted with tar and Shope's papilloma virus was then injected intravenously it would be localized in the tarred skin and produce growths which from the first were malignant. Andrewes, Ahlstrom, Foulds and Gye have tried to produce connective tissue tumours in the same way. Tar was injected intramuscularly and the Shope virus intravenously, and in each laboratory one rabbit of a small series developed a sarcoma at the site where the tar had been injected; the usual effect was a fibroma at the site of injection and a general fibromatosis. Dr. Foulds found that the essential factor was the immediate tissue reaction to the tar, and not the presence of tissue which had been long in contact with tar and might be in a precancerous state. The conversion of fibroma to sarcoma was not again observed, and when Andrewes and Ahlstrom examined their sarcoma they could find no trace of virus in it.

In America it is reported that if 1:2:5:6-benzanthracene is repeatedly injected into rabbits they become much better media for the growth of transplanted Brown-Pearce rabbit carcinoma. It is suggested that substances containing the phenanthrene ring alter the tissues and make them more susceptible to tumour growth.

In New York Woglom discovered that subcutaneous abscesses arising as a complication of experiments with a rat tumour could be serially transmitted by a filtrable agent. Dr. Knox found this agent had an average diameter of about 0.2 micron. The interesting fact is that the virus is found as a contamination of a tumour and is pyogenic.

Dr. W. Cramer and Mr. Hornung, continuing their work on hormones, conclude that there may be a physiological antagonism between oestrone and the hormones secreted by the pituitary acidophil cells. Experiments on mice have shown that the thyrotropic hormone which stops the action of oestrone on the pituitary body and on the mammary gland also prevents in a specially selected strain of mice the spontaneous development of breast cancer.

Strong, of Yale, has found that the inclusion of heptylaldehyde in the diet of mice with mammary cancer causes extensive liquefaction of the tumours, and sometimes complete regression. The heptylaldehyde appears to act on the connective tissue framework of the tumours, and when it was applied to mixed cultures of fowl tumour cells and chick...
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fibroblasts no selective action on the growth of the cancer cells could be demonstrated.

The last section of Dr. Gye's report is concerned with radiation. It has been found that the glycolytic process used by the cancer cell is specifically vulnerable to radiation applied at low temperature. It is stated that experiments give no evidence of any dependence of biological effect on the quality of the radiation used. A given dose of radiation measured in rontigen units, whether gamma, beta or X radiation, produces exactly the same inhibition of retinal glycolysis.

In the Report on Radium Beam Therapy Research issued by the Medical Research Council in 1938, it is stated that the research in 1934-38 was limited to cases of cancer of the mouth, pharynx and larynx, as growths in these are situated in sites accessible to direct examination. From the beginning it was realized that the problem of successfully treating cancer is as much a physical as a clinical one, and a physicist and his staff have been in co-operation with the clinicians.

Stringent rules were drawn up to avoid undesirable effects on the workers and the patient from undue radiation. Charged condensers carried by each member of the nursing staff recorded the amount of radiation received by every nurse each day. There was no single case of damage by radiation to any member of the nursing staff or any of the research staff, and no accidental damage to any patient.

In the past a cause of failure in radium beam therapy has been the inability to assess with accuracy the dose delivered to tissues at some distance from the surface. A great deal of thought and work have been expended in the control and estimation of dosage. Blood examinations in both staff and patients were made at regular intervals and recorded. Every case was followed up and not a single patient was lost sight of.

An attempt was made to treat the primary growth through the lymphatic gland area, so that both might be influenced at the same time. In many cases the enlarged glands disappeared and did not return. This was very encouraging, as the surgical treatment of infected glands in the neck is extremely difficult in carcinoma of the mouth.

The following conclusions were drawn as to the value of the treatment:

1. In cases where the growth is early and localized its complete disappearance can be expected.
2. Where there is secondary involvement of the lymphatic glands in close proximity to the growth, the enlargement of the glands can also be made to disappear.
3. Where both the primary growth and glands are in an advanced and inoperable stage, in a small proportion of patients the disease can be
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made to disappear, and in a large proportion distressing symptoms may be relieved.

(4) When distant metastases have already developed, their growth will be progressive and inevitable, even though in the region treated the disease has been destroyed.

(5) Though it is too early to make definite pronouncements, it would appear that treatment of cancer of the mouth and throat by radium is at least as satisfactory as that provided by surgery or by interstitial radium therapy. It has, further, the great advantage that the results are obtained without mutilation of the patient.

The research staff are now making plans for investigating the treatment of carcinoma of the breast and of the mouth by means of a unit containing ten grammes of radium, which has never been attempted in this country. It will be of great interest to compare the results obtained with a ten-gramme unit with those obtained with a five-gramme unit hitherto used: the dosage will be doubled, the treatment time approximately halved and the biological response may be improved.

Another valuable investigation, plans for which are being made, would be a parallel trial of treatment with X-rays, done with the same accuracy and care as have been given to the radium work, in order to provide a basis for an unbiased comparison of the relative merits of the two methods.

In the Report of the Medical Research Council for 1937-38, just issued, it is stated that there is already looming in the distance the need for studying the therapeutic effects of neutrons and of temporarily radio-active substances, such as radio-sodium, now made possible by the discovery and development of the cyclotron by Lawrence in California. The earlier reports from the University of Berkeley indicate that the biological effects of neutrons are of even greater interest than those of X-rays and gamma rays; and it may be that in the special case of cancerous growth, and allied conditions, neutrons may be of outstanding importance. There is even the possibility that both radium and X-rays will be superseded by the cyclotron in the treatment of cancer by radiations and radio-active substances.

The Council state that Dr. F. G. Spear of their staff is at present in California working with Professor Lawrence on the biological effects of neutrons.

In assessing the facilities for treatment of cancer, the Chief Medical Officer of the Ministry of Health in his report for 1936 points out that it is important to find out the probable number of cases requiring treatment. It is comparatively easy to anticipate the number of cancer deaths as well as their distribution by organs which will occur in a given administrative
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area within one or two years. It is next important also to know to what extent the number of deaths form a reliable guide in assessing the actual patients to be cared for. In the case of cancer of the breast the "natural duration"—in the absence of treatment—is about three years; there will, therefore be three times as many persons suffering from the disease as succumb to it in that year. A similar basis is used for the "accessible" group of organs for which data relating to the natural duration have been acquired; while for the remaining organs a duration of one year is assumed, an incontrovertible minimum. The estimation obtained in this way is a rough one; the effect is to indicate that the number of patients during a given year is 50 per cent higher than the number of deaths recorded for that year. In estimating the number of patients for whom full facilities for treatment are needed, cancer cases may be classed into two groups, (a) those in accessible sites and (b) those in internal organs. The number of cases in group (a), the treatable group, is in the region of 40 per cent of the total number of patients; the estimations just mentioned have been used in determining the adequacy of present facilities for treatment.

From the returns of a number of hospitals the proportion which cancer patients form of the total numbers admitted can be ascertained. It was found that cancer patients formed about 6 per cent in the hospitals with full facilities for treatment and about 2 per cent in the smaller provincial hospitals with no facilities other than operative treatment. Separate enquiries were made at those hospitals devoted entirely to the treatment of cancer and at those large general hospitals partially equipped for radium treatment. The actual numbers could be obtained for the former, but in the case of the latter it was necessary to take figures half-way between those having full radiation treatment and those with none at all. Of the actual cases so estimated it was ascertained that about, or rather less, than 40 per cent belonged to the treatable class.

The figures obtained for all the hospitals were then set against the total number of cancer cases of treatable sites estimated to be in existence during a year. The first deduction made from the figures was that the total number of cancer patients admitted to voluntary hospitals is about two-thirds of the total number of deaths, so that if the number of cancer patients is about 50 per cent higher than the deaths, not more than 40 to 50 per cent of all cancer patients are admitted. For the whole country it would appear that not more than a quarter or a third of all treatable cases are admitted to hospitals in possession of full means for radium treatment.

In order to remedy this state of affairs the Minister of Health feels satisfied—and in this he is supported by the views of the Radium Commission—that the position can only be met by a more active co-operation of local authorities. There should be complete co-ordination between the work of the voluntary hospitals and the local authorities. Treatment
would remain with and be carried out in the hospitals, the centres of X-ray and radium work, while the "field" work would rest with the local authorities. They would be concerned with advice outside the centres (with the help of the staff of the centres), with informing practitioners and the public, of the arrangements for helping and inducing patients to seek advice and treatment, with after-care and "following up." A number of local authorities are now practising one or other of these forms of co-operation, with results so favourable as to encourage their wider application.

In the matter of advice to the public, it is important that the notice of the provision of additional facilities should be in such a way as to encourage patients to seek early treatment. As regards obtaining treatment earlier the British Cancer Campaign through its Central Propaganda Committee is doing work devoted to this particular object.

The Radium Commission stated in their Seventh Annual Report that the facilities for treatment were inadequate, and as the estimates made by the Ministry corroborated this view it was deemed well to attempt a more direct assessment of the situation. Accordingly, an inquiry into the extent to which cancer patients receive treatment was made in 1938 by the Hon. Sholto Douglas for the Ministry of Health, and the results were published by the Ministry in Report 39 on Public Health and Medical Subjects, in December, 1938.

The report shows that patients with cancer can be divided into three groups. The first contains those patients who suffer from the disease in organs for which, under present conditions, treatment is impracticable, e.g., pancreas, oesophagus, lung, bronchus, etc. Such patients form about one sixth of the total cancer patients, and although a sensible proportion attend for advice at hospitals, little or nothing can be done for their relief.

The next group includes patients for whom treatment may be possible, provided they attend at an early stage and adequate facilities for treatment are available. This group comprises over half the total cancer patients, most of whom are affected in the stomach and intestinal canal. About half the patients attend for advice, but only about one tenth obtain any form of radical treatment.

The third group includes patients with cancer of those organs, viz. breast, uterus, skin, tongue and mouth parts, which are amenable to treatment by surgery and/or radiation at almost any stage of the disease, and constitutes one quarter of the total deaths from cancer. Nearly three quarters attend for advice at voluntary hospitals, and over half obtain treatment, but the proportion which attends for treatment at hospitals equipped with full facilities for modern treatment is small and just over one quarter.