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Cancer Research: Its History and Prospects

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Abstract

Of all the invitations one has ever been privileged to receive, I wish you to know that the arrival of your own was a special honour, and a special delight to accept—giving me, among other things, the opportunity to re-visit the house of our ancient Society, and to recall at close hand many happy occasions within these walls some thirty years ago. It was the time of the great Sir Alfred Ewing as Vice-Chancellor, and, in the Medical School, of Sir John Fraser and Sir David Wilkie of glorious memory, whose portraits adorn your walls. We generated then, as doubtless you generate now, abiding affection for Edinburgh and its University, and not only affection but I confess it, sentiment, for our Royal Medical Society. Reading the leading article in the second number of Res Medica, I have been greatly struck by its closing sentences: "At a time when religions, cultures and individuals are menaced by nuclear weapons and foreign ideologies, living traditions assume an importance never envisaged by their inaugurators. Let us then foster unity and friendship and be worthy heirs of our heritage." This is the ever-renewing and ever more significant function of the Royal Medical Society, and I esteem the great honour of inaugurating your two hundred and twenty-second Session. I mention these things to show how it is and why, that I received your invitation with such pleasure and gratitude.

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CANCER RESEARCH: ITS HISTORY AND PROSPECTS

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Inaugural Address of the 222nd Session, read before the Society on 10th October, 1958.

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I have taken as my subject the history and the prospects of cancer research. It could be regarded as a morbid one, but I hope to show that this is not necessarily so; on the contrary, that the history of the field is romantic and inspiring, that its present state is active and exciting, and that its future—although by far the greater part remains to do—is full of hope and promise.

Cancer research can be regarded from two aspects—the purely medical, as a great endeavour directed to the solution of a human problem; and scientifically, from the unique character of the disease, as an integral part of modern biology. It is unique since its basis lies in a permanent accession in the growth of cells. Its history has largely been coterminous with that of the microscope, permitting the development of the cell theory, which has been described as one of the greatest conceptions of the human mind, and which, although it had many precursors, was finally established as recently as the early part of the nineteenth century.

It is often said that the cancer cell has acquired the power of unlimited growth. This is strictly not so, since most normal cells are equally capable of unlimited growth in appropriate conditions. More and more certainly, cancer appears rather as due to the release or unmasking of that growth potential which cells all along possess, although exquisitely restrained. The mechanics of cell division appear devised to effect an equal distribution. Yet soon in development is superposed the mysterious feature of differentiation, while the rate of growth declines. Even in the adult, however, cell

division continues, either temporarily as in the healing of wounds, or continuously as in the tissues of the bone marrow, intestine and skin. The main feature here is a matchless orderliness and precision. In the words of Dr Isaac Watts in one of his hymns, "Strange that a harp of a thousand strings, should keep in tune so long." Sooner or later, however, a single cell may become transformed to a cancer cell, with altered growth properties which are now and henceforth no longer subservient to the needs of the body, but independent and frequently autonomous. The liability to this change appears inherent in all cells capable of growth. It is not surprising, therefore, that we should find evidence of it throughout the whole of the plant and animal kingdom, not only in historic but also in pre-historic times.

So far we have spoken of the nature of cancer. What of its cause or causes? Modern cancer research largely dates from the time of Rudolf Virchow, whose *Die Cellularpathologie* was published almost exactly one hundred years ago. Remembered for his dictum *omnis cellula e cellula*, he applied the cell theory to pathology, and inaugurated several decades of investigation of the microscopical structure of cancer in man and animals, carried out first in the great schools of Germany and then the world over. Although historically necessary and important, this was not, however, sufficient. Towards the close of the century a need became ever clearer, namely, for the use of the experimental method. In this country, the new outlook led in 1902 to the establishment of the Imperial Cancer Research Fund, and in 1909 to that of the Research Institute of the Cancer Hospital in London. The first director of the former institution was E. F. Bashford, who with great genius and foresight, and with the support of a small but brilliant staff, was able within a brief ten years to lay the main foundations of the whole subject, and to forecast its likely development and requirements for many further years ahead. All this helped to prompt, or was accompanied by, similar developments in the United States, in Europe, and in Japan.

Although purely medical methods alone were to prove insufficient, it should be noted that the first and vital clues arose from observations made in the field of occupational and industrial medicine. Towards the end of the eighteenth century, Sir Percivall Pott had described the special liability of chimney sweeps to cancer of the scrotum, and had traced the cause to contamination of the skin with soot. With the industrial revolution came many more examples, mainly due to occupational exposure to mineral oil and tar. A notable case was the so-called "paraffin cancer" in the Scottish shalefield, described by the celebrated Joseph Bell, of whose association with the Royal Medical Society we are justly proud. Experimental proof that mineral oil, coal tar and pitch do in fact induce skin cancer had, however, to be long deferred, indeed until 1915, when Yamagiwa first produced cancer artificially through chemical means, by applying coal tar to the skin of the rabbit ear. Coal tar being a complex mixture of a great host of chemical individuals, the search then began for the responsible agent or carcinogen. In the early 'twenties, Bloch in Zurich adduced evidence that the agent might be a complex hydrocarbon, that is, a compound containing hydrogen and carbon only—and virtual proof of this was later obtained by my own predecessor, Sir Ernest Kennaway, at the Cancer Hospital. Through his work and that of his school, the picture gradually emerged of carcinogenic substances built through the conjugation of benzene rings.

Early in these investigations, it was repeatedly noted that cancer-producing tars exhibited the property of fluorescence in ultraviolet light, that is, to absorb invisible light of short wave-length, and to emit visible light of longer wave-length. In 1927, W. V. Mayneord, again at the Cancer Hospital, took

the matter decisively forward when he indicated that the fluorescence spectra of such tars showed qualities which appeared to be characteristic. This spectrum of cancer-producing tar proved to be, in Kennaway's words, "the single thread that led all through this labyrinth," and it soon enabled him, and his colleagues, to track down the carcinogenic agent. Since it was already suspected to be a complex hydrocarbon, the next step was to examine the spectra of those polycyclic hydrocarbons already known in pure form, and constituted from the fusion of various numbers of benzene rings. Very shortly, Hieger was able to make the key discovery that *1:2-benzanthracene*, (comprising four such rings), also possessed the characteristic spectrum. By a curious accident, Clar in 1929 had just described the synthesis of the related hydrocarbon containing five fused rings, (*1:2:5:6-dibenzanthracene*), and in the same year Kennaway and Hieger proved this substance to be carcinogenic in mice—the first pure chemical individual to be recognised as possessing this property. The fluorescent spectrum was also used to great purpose in the isolation of the naturally-occurring carcinogenic agent from pitch. This proved to be another pentacyclic aromatic hydrocarbon, namely *3:4-benzpyrene*, which Cook and Hewett were soon (in 1933) to prove by synthesis. In the same year, Cook and Haslewood produced *methylcholanthrene* from a bile-acid, so raising the whole question—still undecided—whether traces of highly potent carcinogens can be formed *in vivo* from perturbations of the normal metabolism of steroids. A chief result of all this work was eventually to provide an amazingly satisfying and complete picture of the relationship existing, within this series, between chemical constitution and biological action.

In the intervening years, many older chemical classes had been uncovered, in no way related to the cyclic hydrocarbons, but equally endowed with carcinogenic qualities—various aromatic amines, especially those involved in the causation of cancer of the bladder; a host of azo dyestuffs with the special propensity to evoke tumours of the liver; a series of aminostilbenes with very diversified carcinogenic properties; and many others. To these we must add a great range of purely physical agents, including ultraviolet radiation itself, X-rays, radium and thorium, and a host of radio-isotopes arising from the atomic energy programme, especially radiophosphorous, radioiodine and radiostrontium. Of late we have also recognised the carginogenicity of many macromolecules and plastics, and the special function in carcinogenesis which may be played by the metals, as also the role of many biological agents, e.g. those viruses responsible for the induction and propagation of certain tumours in animals (although not so far in man)—topics any one of which could easily exhaust a whole lecture in itself.

In none of these cases have we precise knowledge of the mode of action, or of the site at which it is excited within the cell. Only in the past few years have there come certain hints, through the discovery of carcinogenicity in yet another chemical class, namely the nitrogen mustards—substances developed in the Second War for the purpose of chemical warfare, and nitrogen analogues of that sulphur mustard or "mustard gas" which had been used in the War of 1914-18. The nitrogen mustards have the advantage of relative chemical simplicity, with features which are suggestive, or even indicative, of possible modes of action. The action upon dividing cells is highly direct, leading to cytological abnormalities indistinguishable from many which can equally be produced by ionising radiation. On this account they are not unreasonably described as radiomimetic, and it is certainly remarkable that just as X-radiation is employed in the treatment of cancer, so also can some of the mustards, in the palliation of certain forms at least. Contrariwise, just as X-rays can be cancer-producing, so also can the

mustards. In many cases the tumours so produced bear signs—as a kind of imprint—that the action has involved the nuclei and chromosomes. A certain extent of chemical reactivity is required, suggesting again that the biological end-result may depend upon reaction with some cellular component so far undefined. The main features of the nitrogen mustards is their possession of two or more haloalkyl side-chains. Within the series this indeed appears to be a requirement for biological activity, and led to the proposal that activity might in fact depend upon chemical cross-linkage, as for example between the contiguous linear macromolecules of the chromosomes themselves. Although this hypothesis is now known to be unduly simple, it proved tremendously fruitful in development, leading for example to the application of much knowledge already available in the field of cross-linking agents in textile technology, and hence to the rapid discovery of other series with similar biological effects—epoxides, polyethylene imines and dimesyl compounds—now classed under the general heading of biological alkylating agents.

The exact nature of the biological receptor is still not known. It is very probably genetical in function, as reaction within the nucleus and upon the chromosomes might infer. However, such reaction would certainly introduce widespread repercussions in the cytoplasm, and direct action by certain carcinogens upon the organelles of the cytoplasm is by no means excluded. Notwithstanding, a prominent candidate for the seat of action of the carcinogenic alkylating agents is without doubt—and for many reasons although none is as yet decisive—the deoxyribonucleic acid of the chromosome structure, as the chemical basis of cell genetics and heredity. A great impetus has been given to these studies by the proposals for nucleic acid structure put forward by Crick and Watson—of the bonding of pyrimidine and purine base pairs to yield essentially superposable structures, and of the complementary disposition of these as bridges in a double helix of phosphate-sugar chains; and we already have some precise chemical information as to the action upon such a structure both of ionising radiations and of the ions yielded by alkylating agents. But further advance must largely depend upon our deeper knowledge of chromosome structure. While waiting, we can gain much through the use of what is still the most favourable material—namely the giant chromosomes of the salivary gland of the fruit fly *Drosophila*—in studies of the chemical basis of biological mutation generally, of which carcinogenesis may be a special case. Acting upon such material, the alkylating agents frequently produce changes of the nature of deletion, and this, with other considerations, has led to the view that cancer causation could be due to combination of the agent with nucleic acid, so leading to defects in its synthesis or structure. This process would interrupt the essential precision of the nucleic acid, and prevent the formation of certain protein molecules (and especially perhaps growth-regulatory enzyme-proteins vital to the control of normal cell division), for which we know the integrity of the nucleic acid structure is necessary and responsible. In the case of the carcinogenic hydrocarbons and azo-dyestuffs, there is also evidence that the same deletion of key proteins can be brought about by combination of the carcinogen with protein molecules themselves, directly.

We therefore approach the view that carcinogenesis is a process of biological mutation by loss, and that there is no true acquisition of a new growth property on the part of the cancer cell, but rather the unmasking of the growth potential which its normal precursor had all along possessed. The general conception has still to be tested, and could clearly have the widest implications. There is an increasing number of diseases recognised as due to enzyme deficiency, and some of them can be controlled by restoring the defect through a kind of substitutive chemotherapy. It well may be,

in the future, that cancer too will fall in this class, and become amenable to control through a re-imposition, from without, of that growth regulation which the cancer cell itself has lost forever. At any rate it can fairly be said we are at least approaching certain correlations, between the reactive properties of given carcinogens, the places at which and the methods by which they combine in the cell, and the permanent alterations in growth behaviour, which come about as the result. Although so much remains to do, the story is great and growing. When one day it comes finally to be told, it will be seen to have meaning far beyond the sphere of medicine alone, and to be in part a model of what can be achieved by the human mind through the interaction of biology, chemistry and physics.

I end as I began, with thanks to the Society and all its members for this kindly privilege. I also wish to record special indebtedness to my colleague Mr K. G. Moreman, and to the officers of the Society for indispensable assistance. May the Society enjoy strength and prosperity not only in the present new Session, but in all those which lie ahead, in a future which we are confident will continue that unfolding of the art, science, and achievements of Medicine, towards which the Society itself, in its long history, has made no mean contribution.

Floreat Res Medica!