Certain biological aspects in the general pathology of malignant new growths / by J.A. Murray.

Certain Biological Aspects in the General Pathology of Malignant New Growths.

By J. A. Murray, *M.B.*

From time to time biologists have turned their attention to some of the problems which cancer presents, but their contributions to the subject have not been accepted as final. The limited scope of the individual investigators may well be the principal reason for this want of correlation between the different lines of work. The investigations of the Imperial Cancer Research Fund have been directed by the conviction that it is essential, if progress is to be made, that the facts from widely distinct fields of inquiry should be focussed on the essentials of the problem, and conclusions apparently warranted by one set of observations must be controlled by all the others.

The following different lines of inquiry seem to be of importance at present:

1. Pathological-anatomical, including gross anatomy, as well as histological and cytological investigations.
2. Zoological distribution, including ethnological distribution.
3. Statistical investigations—age distribution in correlation with zoological distribution.
4. Experimental investigations. Transmissibility. Powers of growth of normal and malignant tissue.

Malignant new growths, in common with benign, increase their characteristic parenchyma entirely from their own resources. As soon as a malignant new growth is recognisable as such, it is marked off anatomically and physiologically from its surroundings. This phenomenon, now well established, is sufficiently remarkable when it is borne in mind that, histologically, the independent tissue may be indistinguishable from that among which it takes its origin. To a recognition of this fact is due the acceptance accorded to Cohnheim's hypothesis and all its variants. These variants were introduced because of the necessity that was felt to account for the close dependence of the type of growth on the characters of the surrounding tissue, especially when the latter presents well-marked differences at different periods (Thiersch, Ribbert). They are all attempts to account for the behaviour of malignant new growths as independent new organisms, and, whatever acceptance we may accord to the various hypotheses, the fact they seek to explain is incontrovertible. In discussing the experimental investigations some reasons for considering these hypotheses as inadequate will be referred to.

The cells of malignant new growths increase in number by division. Amitosis certainly occurs, but mitotic division is by far the commoner, especially in fully developed tumours. Multipolar mitoses are common, but not universal. The active growth and extension of the malignant tissue, as manifested at the growing surfaces of the malignant new growths we have so far examined, is effected by cell-divisions, which, so far as they are mitotic, conform to the ordinary type met with in early development. Apart from multipolar divisions, the number of chromosomes entering the equatorial plate is found constant in each species, and they undergo the ordinary longitudinal splitting. Passing from the growing margin towards the older parts of the growth two sets of changes occur. Many cells undergo the characteristic histological changes peculiar to the tissue among which the tumour has arisen, while others prepare for further mitosis. In some of these the resulting mitosis is characterised by the presence of bivalent

chromosomes (heterotype), in number half that found in the younger parts. From the position of these heterotype mitoses in relation to the growing surface of the tumour in which they occur, they must be regarded as a late phenomenon in the life history of the cells, contemporaneous with the histological differentiation going on around them. We have not found evidence of continued proliferation of the immediate descendants of the heterotypical division, and the analogy of animal spermatogenesis suggests that the heterotype initiates a terminal phase in the life history of the cancer cell as in the spermatocyte.

From a consideration of these facts the most divergent conclusions have been drawn. Professor Farmer and his colleagues, who first described the occurrence of heterotypical mitoses in malignant new growths, consider that we have here a transformation of somatic tissue into a kind of reproductive, 'gametoid,' tissue, which, *qua* its gametoid character, is independent and capable of unlimited further growth. This view of the nature of the change which marks the distinction between somatic tissues and malignant new growths had already been advanced by Beatson as a result of clinical considerations. Against this view the general objection may be raised that, while it would explain the occurrence of heterotypical mitoses in malignant new growths, as regards the powers of growth and self-propagation and independence which they manifest it is no explanation at all.

In the vertebrates, where malignant new growths have alone been found up till now, we have no evidence that gametes, or the tissue which precedes them, possess powers of growth at all comparable to those seen in cancer. The analogies drawn from the vegetable kingdom all concern the interaction of independent organisms, not of different tissues of the same organism.

When, however, the attempt is made to attack this problem by experiment, and artificial propagation of reproductive tissue in animals is tried, the results are in no way different from those obtained with other tissues. The power of independent growth is very limited, and it is found that the power of regeneration of which the testis is capable (along with the thyroid) is confined to the stages before differentiation of gametes has commenced.

The power of propagation of malignant new growths is much greater. While only possible within animals of the same species as that furnishing the initial growth, it is found that the cells can establish themselves and produce masses of tissue as large as the primary growth in successive animals through long periods.

While studying the changes which ensue immediately after transplantation in a tumour of the mouse, we observed nuclear changes which presented a close similarity to a conjugation process. Subsequent observations of an extensive material, embracing over 1,000 tumours of all ages, obtained from three different primary growths, have tended to confirm this interpretation. Thus the same sequence of nuclear changes is again found in later stages, all evidence of its occurrence being wanting in the interval. These observations harmonise very well with the appearances which this tumour presents as it increases in size. Numerous secondary centres of growth are always found around the periphery of older tumours, and these secondary masses may in time outgrow that which preceded them. At once the suggestion arises that the cells which conjugate are those which have passed through a reducing division, but till the complete cycle has been elucidated the thesis outlined above must remain a working hypothesis. It is in harmony with what we know of malignant growths, and renders secondary assumptions unnecessary.

The relation it bears to the question of the initiation of the cancer cycle may be emphasised by a short reference to another line of inquiry—that, viz., of the age incidence of malignant new growths. The life cycle of all the higher animals commences by a fertilisation process, on which cell-division ensues, and the rate of this cell-division continually diminishes as life proceeds. Its gradual cessation manifests itself in the onset of old age, and along with this diminishing power of proliferation there is an increasing liability to malignant new growths. The hypothesis outlined above is an attempt to account for the entrance of a new growth cycle without doing violence to what we know of the general course of cellular activity. It involves the assumption that the ordinary tissues of the

body in the terminal phases of their growth may undergo changes by which a conjugation process is possible. Whether this process is effected or not would then determine whether a new cycle of growth be initiated and a malignant new growth result.

In conclusion, an appeal may be made to working zoologists to be on the alert for malignant new growths and allied conditions in the lower animals. Every observation in this direction has a positive value. So far no case of cancer has been found in reptiles among vertebrates, and none at all in invertebrates. When one considers how frequently cytological studies have been undertaken in the latter, it will be appreciated what importance would attach to the discovery of cancer in lower forms of life.

PRINTED BY
SPOTTISWOODE AND CO. LTD., NEW-STREET SQUARE
LONDON