STUDIES ON TUMOUR FORMATION

BY
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FOREWORD

G. W. NICHOLSON'S twenty *Tumour Studies* which appeared in *Guy's Hospital Reports* between 1922 and 1938 are classics. Not only do they contain a wealth of original observations recorded with meticulous accuracy and beautifully illustrated by drawings from Nicholson's own hand, but they abound in cogent reminders that pathology is a branch of biology, in devastating and amusing criticisms of ill-founded speculations, and in apposite quotations from philosophy and the classics.

In a letter to Nicholson acknowledging a reprint of one of his Studies in 1934, Sir Arthur Keith wrote "there is science and poetry combined in it—to say nothing of philosophy"; and again, referring to a particularly clever play on words with which Nicholson scoffed at a piece of foolish speculation, "you could match G.B.S. at his own game!" He who seriously reads these Studies for the first time can be assured that, along with their abundance of reliable factual information, he will find also much that is arresting, piquant and entertaining; Nicholson was a great philosopher and thought-provoker as well as a great biologist and pathological anatomist.

The range of subjects covered in this series of papers is astonishing—as the index to the printed volume will show. Topics which are dealt with here more authoritatively and with a stronger basis in general biology than in any other writings include the general structure of tumours, minor malformations, heterotopia of tissues, metaplasia, mixed tumours, and the teratomas. Here also are the best refutations of many false hypotheses, for example that of Cohnheim on "cell rests", of Grawitz on renal tumours, and of Wilms on teratomas. Here is pathology written by a man with an extensive knowledge and keen appreciation of recent advances in experimental biology and embryology—who knew the work of Roux, Dreisch, Spemann, D'Arcy Thompson, Child and Needham as well as he knew that of his fellow pathologists. Here is pathology to read and read again and ponder over.

After the end of the recent war Nicholson was urged by several of his friends to benefit pathology by republishing his collected work in book form, but he was deterred from doing this by the prospect of the work involved in amending those parts of his early papers in which later experience had caused him to modify his views. Towards the end of 1948, however, he had almost made up his mind to undertake the task, but his death came before he had commenced it. In the present volume, therefore, his *Tumour Studies* are reprinted in the original form without any attempt to modify passages which he himself might have wished to change. In truth, they contain remarkably few passages that really call for amendment; and it is better that these should remain as Nicholson first wrote them than that meddlesome attempts at improvement should result in misinterpretation of his more mature opinions.

All of Nicholson's drawings also reappear here. The reproduction of some of these was difficult because all the originals and some of the blocks had been lost,

so that copies had to be made from the printed page. However, the publishers have spared no effort or expense in carrying out this task and have achieved well-nigh perfect replicas of the original illustrations.

Nicholson's former colleagues at Guy's Hospital, in their desire to perpetuate his memory, could not have conceived a more appropriate way of doing so than by the republication of his papers from their Hospital Reports. This is not only a fitting memorial to a great man who was too little known in his own lifetime, but it also provides, in easily accessible form, a classic of tumour research which will be a great boon to all pathologists present and to come.

RUPERT A. WILLIS

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October, 1949.

INTRODUCTION

NICHOLSON has left a lasting memorial in pathology, not only by his many original and scholarly contributions, but also by providing a shining example of the qualities required for the scientific pursuit of knowledge. These have served as an invaluable guide to his colleagues and pupils. Besides being endowed with a critical and powerful intellect, he acquired an independence of thought which made him a most stimulating teacher to those who were willing to follow the austere path of intellectual integrity which leads to the discrimination between knowledge and ignorance. His intolerance of dogma when based entirely on authority and lacking adequate scientific evidence, was sometimes disconcerting to the student, but to those who knew him intimately and who were to profess pathology, it was both a refreshing and wholly necessary attitude, recalling to mind the tradition of the Renaissance in the words of Leonardo da Vinci "He who adduces authority as support in a discussion, uses his memory and not his intellect." That he was cognisant of what authority had to say, can be seen from the erudite scholarship of his own work and the impartiality with which he sifted the evidence was undeterred by the notability of a popular name.

Nicholson's methods were the classical ones of observation, which was always of an elegant accuracy, accompanied by detailed description of the phenomenon in unequivocal language; verification, which frequently had to satisfy not only the discipline of pathological principles but those of other sciences such as physiology, embryology and biology which often confirmed his original interpretation and finally came the generalization in the form of a scientific principle which became a landmark and which still serves to guide students of oncology. His diligent pursuit of these methods throughout his active working life of forty-two years and which brought him such consistently fruitful results was a model of scientific endeavour carried out with calm enjoyment and without any apparent spiritual or intellectual "travail".

The source of most of his material was the surgical wards of Guy's Hospital, to which he was Clinical Microscopist and which he served with almost religious devotion. As a practising pathologist, in the diagnosis of tissues he was unsurpassed. His vast experience of morbid histology and the accuracy of his diagnosis, made his opinion sought after by colleagues from all over the world and his final judgement was invariably justified by future events. The time and thought which he gave to the study of a particularly difficult specimen was a measure of his humane feeling and of his determination to give of his best. His facility with the microscope was apt to astonish his junior colleagues who, greatly impressed by what appeared to be a supernatural insight, became sceptical of their ability ever to achieve such a high standard of accuracy. As the daily sessions at the microscope with the master went on year after year, they acquired something of his excellence and they realized the importance of experience and how fortunate to have gained it with such a teacher. Another lesson to be learnt from him was humility—the acknowledgement

of ignorance was no crime but should act as a stimulus to attempt the removal of the defect. The clever but evasive answer was condemned for its immorality, since it might mislead the ill-informed and satisfy the unscrupulous. It was a hard but noble school, because it taught that there could be no compromise with expediency or with hypothesis and that the truth was more readily realized by the objective examination of the evidence, the nature of which he was fearless in expressing.

Although he had a retiring nature and a personality which appeared to be aloof and which at first sight gave one the impression of reserve if not of haughtiness, it contained a warm and generous character, seen only by his few intimate friends, to whom he was the calm and wise philosopher.

He was readily accessible to colleagues and students whom he received with unfailing and delightful courtesy in keeping with his spare dignified figure. He avoided the limelight and was contemptuous of flattery or publicity, preferring to allow his work to speak for itself. His influence on his contemporaries might have been greater had he chosen the more populated thoroughfares of congresses, committees and boards, to which he was frequently invited, but crowds disturbed him and majority opinions, which too frequently are a compromise even in scientific circles, failed to satisfy his own high standard of values. He preferred and was content to pursue his often solitary way with unwavering intent of purpose, seeking the truth and well satisfied with its discovery, regardless of the consequences. He was indifferent to personal possessions, other than his books and specimens and almost oblivious of the economic and social upheavals of our time, thereby preserving that clarity of thought and serene search for truth which is the traditional hall mark of Western European culture, which cannot survive without such men as Nicholson.

S. De NEVASQUEZ.

Guy's Hospital
London.

October, 1949.

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WE ARE indebted to the Guy's Hospital Reports Committee for permission to publish the papers of the late Professor G. W. de P. Nicholson, which are reprinted from *Guy's Hospital Reports*.

The references to these papers in *Guy's Hospital Reports* are given hereunder.

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CHAPTER 1

INTRODUCTION

TUMOUR formation must ultimately depend on one of two causes. The cell or cells from which the neoplasm arises must either be abnormal *ab initio*, or else some external stimulus must induce a normal cell or group of cells to proliferate abnormally. In default of certain knowledge both these views have been held and have given rise to a multitude of theories. To assume that the cell has always been abnormal is a very comfortable view to take, since every phenomenon of neoplasia is readily explained by its aid. But, in the present state of our knowledge, it is nothing more than one of the innumerable ways of begging the question. The thing to be explained forms a part of the explanation. Besides, it shuts the door most effectually on every attempt at investigation. We know nothing about the fate of abnormal cells. Multi-nucleated ova have been frequently described, and I have myself seen them in apparently healthy adult ovaries. A large number of abnormalities of the spermatozoa are known. But can these cells conjugate, and, if they can, what will be the result? Even in the lower animals, in whom it is possible to induce polyspermy, the embryo perishes in the blastula stage. Such experiments do not help us at all in our attempts at finding an explanation of tumour formation, a process occurring in an otherwise normally developed individual. I am filled with amazement at the fact, which surely is the most wonderful thing in a very wonderful world, that the huge majority of children that are born are normally developed and that they are not formless lumps of flesh, and that gross abnormalities, as we call them, deserve their name and are not the rule. Ought we not to try to show why things so very generally go right, rather than why they occasionally go wrong? Surely this suggests that the cell from which the embryo develops is practically always a healthy one, and that it will grow into a healthy individual if it gets the chance, i.e., unless its development is interfered with by some abnormal stimulus. What applies to the whole, applies to its parts—when there is an abnormality, it has a cause external to itself—and as tumour formation is essentially an abnormality of growth, it applies to it as well. I shall therefore say no more of the theories that postulate a *vitium primae formationis*.

Nor do I intend, for the present, to say much about the other theories, those that have been woven around the second possibility, that tumour formation is due to a stimulus external to the cell. They are all good in their way and contain a grain of the truth. When pressed home, however, they all fail. The reason is not far to seek. We shall find it if we attempt a definition of neoplasia. Let us go to the text-books for this purpose. Thus, Adami (1909), after pointing out that "too often have theories as to the causation . . . entered into the definitions," adopts C. P. White's statement that a "tumour proper is a mass of cells, tissues or organs resembling those normally present, but arranged atypically. It grows at the expense of the organism without at the same time subserving any useful function." Ewing (1919) defines a tumour as "an autonomous new-growth of tissue."

MacCallum (1918) is more cautious. He says that it is only possible to attempt a definition of tumours after a survey of their characters, and proceeds:

> "In the meanwhile it may be said that they are masses of tissue resembling, but not perfectly identical with, the normal tissues, which grow without any regard for the laws which govern and restrain the growth of normal tissues. They are supplied with blood-vessels and a sufficient supporting framework by the host, and derive their nourishment from the circulation of the host. Therefore, like any parasite, they are harmful to the person in whose body they grow; but the injury which they do becomes intolerable when they not only absorb this essential nourishment, but also invade and destroy the normal tissues."

As one of the principal objects of these studies is an attempt to show that these and similar statements are not true definitions, since they do not define, I will for the moment rest content with pointing out that Adami's adopted definition most certainly includes all malformations, not excepting hemi-acardiac parasitic monsters. If Ewing's definition holds good, then the foetus *in utero* is a tumour. We shall see, as we proceed, how near MacCallum comes to a definition. The reason why these definitions break down lies in the nature of tumours. In no essential character do they differ from the other tissues of the body.

In conclusion, I shall attempt to develop my subject by the aid of the material that I have personally examined, and employ my knowledge of the literature merely as an aid and as a check on hasty conclusions. Many important instances pro and con will therefore be necessarily omitted, for my material, although far from small, is still smaller than I could wish. The alternative would have been to have entered into a full discussion of the literature. But this is almost overwhelming. The first course is, I believe, the better of the two. It is certainly the more agreeable and much the shorter.

THE MORPHOLOGY OF TUMOURS

Tumours, as we have seen above, are spoken of as masses of cells, resembling those normally present, but arranged atypically. They are autonomous, and grow without regard for the laws which govern the growth of normal tissues. They are supplied with blood-vessels from the host, and since they derive their nourishment from his circulation and therefore grow at his expense, they, like parasites, are harmful to him. At the same time they subserve no useful purpose.*

It is but fair to state that these sentences are interdependent and that they must not be analysed separately. The penultimate, for instance, can be made to apply (saving the deduction) to the liver or any other organ quite as readily as to a tumour. But I venture to doubt their accuracy even when taken together. Many tumours are very typical in structure, and a great many quite as much so as many malformations. They are certainly autonomous, but so are all the organs of the body. That they grow without regard for the laws that govern the growth of normal tissues I flatly and most emphatically deny. Function is intimately connected with structure, and we shall see that many of the more typical tumours are by no means without function. My present object is to compare the structure of tumours with

* The second part of MacCallum's last sentence (*vide* Introduction), does not apply to all tumours and therefore need not concern us here.

that of other tissues and organs of the body, and to show that, far from being atypical in every case, some of them surprise us by the degree of typical differentiation they attain.

The reason is obvious why such opinions as those enumerated above are held. Tumours are usually harmful. The majority of the investigations carried out on them have as their aim the discovery of the readiest means of getting rid of them and of prolonging the lives of the individuals afflicted with them. The view that is taken of them is therefore biased. This is a mistake, as it is only by adopting the point of view of the tumour, or at least an absolutely impartial view, that we can hope to understand its structure and functions completely. Not until after a full understanding will have been obtained, can we hope successfully to tackle the problem of how to abolish tumours.

If a large number of tumours be examined, the fact is quickly revealed that they are built up on the same plan as the tissues in which we assume that they arise. Not only do the individual cells often closely resemble the corresponding normal

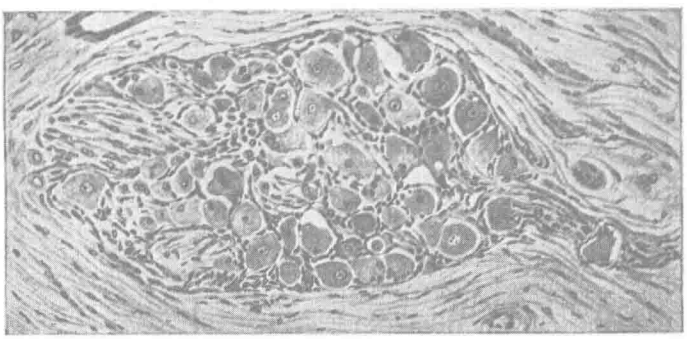

FIG. 1.—Ganglion from retro-peritoneal teratoma of a child of three months. (× 180.)

ones, but their mode of growth and the manner in which they are grouped to form tissues and organs is sometimes remarkable. This is obvious in most innocent slowly growing tumours, and is often apparent in malignant ones as well.

Fig. 1 has been drawn from a large retro-peritoneal teratoma of a child of three months. It represents a well-formed, though not fully-developed and matured ganglion. Differentiation has advanced farthest on the right side of the drawing. Here there are very perfect ganglion cells, some of which contain a brownish pigment (which I have not attempted to reproduce). They are surrounded by definite sheaths, and nerve fibres issue from several of them. These run to the right, where they are collected into a nerve bundle, near the beginning of which there is an isolated ganglion cell. Towards the left of the figure the ganglion cells become smaller and differentiation is still taking place.* I am not sufficiently familiar with the appearance of the developing nervous system to assign to this structure the

* A comparison of Fig. 1 with Fig. 378 of Schaefer's *Text-Book of Microscopic Anatomy* (1912) shows that the differences between them are not great.

exact period of embryonic life to which it corresponds most closely, but I feel sure that it is one of the later weeks. We must remember that the child died very young and that its teratoma had lagged slightly behind in its development; not very much, however, as will appear in a future paper, in which I hope to describe this interesting specimen at some length. I am justified in claiming that it is more than a mass of ganglion cells in a teratoma. It is a ganglion corresponding in its development to one of the later weeks of embryonic life.

Since I am dealing with teratomata, I may mention that they contain a surprising number of tissues. I believe I am right in saying that all the principal organs of the body have been described in them, with the exception of the reproductive cells (Ohkubo, 1908). Even such specialized organs as Pacinian corpuscles have been recorded on more than one occasion (Nakayama, 1905). I myself have seen a plexus of Auerbach on the intestine of an ovarian "dermoid"; also a thyroid and thyroglossal duct. I shall say no more about teratomata here, only this: they, more than other tumours, emphasize the fact that the majority of neoplasms, if not all, have an organoid (Albrecht, 1907) structure, and refute the statement that they grow without regard for the laws which govern the growth of normal tissues. It is only by regarding tumours as aborted organs that we can hope to understand their structure and their growth and development. It may even be that by their aid a clearer insight will be gained into some of the problems of normal development and growth.

I have just said "aborted organs." That a tumour sometimes copies a perfect functionating organ very closely indeed in its structure, is shown by my next specimen. It is of sufficient interest to deserve a short description. The patient, a married woman of twenty-seven, mother of several children, was admitted under Sir Alfred Fripp (who has kindly allowed me to use the case), for a rounded, firm, freely movable, non-adherent swelling of the left breast, which she had first noticed some eight months before, during her last pregnancy. Since then it had steadily increased in size. The baby, at the time of her admission to the hospital, was four weeks old; it has not been breast-fed. There has been no discharge from the nipple. The tumour was easily enucleated, since it was surrounded everywhere by areolar tissue and attached to the substance of the breast by its vessels at one spot only. The specimen measures 8 by $7\frac{1}{4}$ by $4\frac{1}{2}$ cm. in its largest diameters. It is roughly egg-shaped in outline, but is considerably flattened in one dimension. Its surface is smooth, except for a few slight irregular prominences. It is surrounded by an envelope of loose areolar tissue, in which a few small lobules of fat are enclosed, together with an artery which, after running for some distance in a shallow groove on its surface, disappears by entering its substance. It is firm and elastic in consistency. Its colour is mottled, white and pink, with numerous small bright yellow and orange areas, surrounded by bands of haemorrhage. These become confluent to form large, very irregular patches, which are slightly raised above the surface and are most numerous on one side of the specimen. They are due to necroses, and do not concern us here. On being cut open, the tumour is found to consist of an outer fibrous layer, which forms a distinct capsule of more or less concentric laminae. It varies greatly in thickness, and sends several prolongations into the substance of the tumour, one of which is much broader than the others. The prolongations form a meshwork of fibrous septa, and enclose rounded and oval

masses of a softer greyish tissue, which are imperfectly divided by fibrous bands, and appear to be built up of numbers of small rounded nodules. (Some of these masses are yellow and necrotic and surrounded by haemorrhage.) A few small cysts are enclosed in the substance of the largest fibrous septum. They average 5 mm. in diameter.

Fig. 2 illustrates the structure of this specimen. It was drawn from somewhere near its centre. It shows parts of several mammary lobules in an early stage of lactation. They are large, but the biggest of them, fully three-quarters of which is represented, is much smaller than a good many of those of a lactating breast I have compared it with. Owing to their secretory activity, the majority of the tubules are dilated and their epithelium flattened, but a good many small resting tubules are

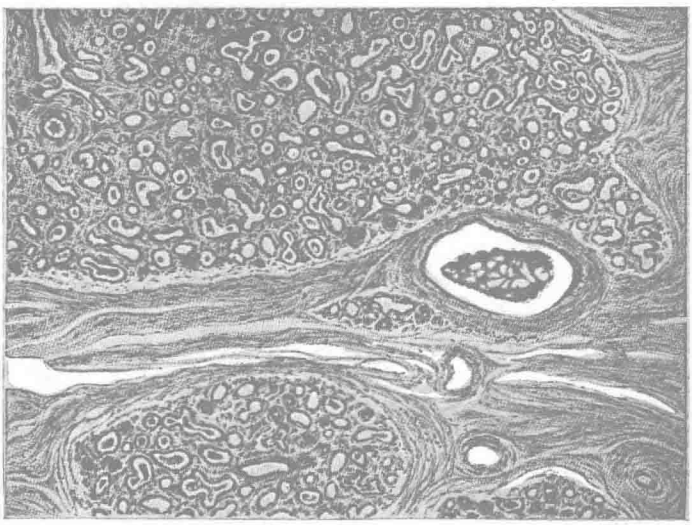

FIG. 2.—Lactating adenoma of breast. (×80.)

scattered about. Several small intra-acinar ducts can be seen. The stroma of the lobules corresponds to that of a normal breast, and so do their contours and the fibrous tissue that surrounds them, in which there is a duct filled with secretion. All the sections examined, except where necrosis had occurred, showed precisely the same structure, except that in some of the lobules there were more resting tubules, whereas in others there was greater activity. A duct was seen to enter the periphery of a lobule. The broad septum described above showed the usual appearances of a chronic mastitis, with atrophy of the lobules and moderate proliferation and dilatation of the ducts.

I could find no evidence of a duct in the areolar tissue around the tumour. There were present a few atrophied mammary lobules, which still retained evidences of secretion.

We have here a tumour which is independent of the breast, but which imitates the histological structure of that organ in the most complete fashion, and shows

not the slightest signs of excessive or atypical, or, in other words, blastomatous growth. Secretion, as far as can be judged, had been going on in a physiological manner. The presence of resting tubules among the active ones is perhaps the most interesting of all its features, since it suggests a very delicate functional adjustment and balance of our tumour.

To name it a fibro-adenoma with an albuminous and fatty secretion conveys no meaning. We can only appreciate the structure of this specimen when we look upon it as a lactating breast. The question therefore arises: Is such a perfect organ as this appears to be a tumour, or is it an accessory lobe, that has somehow become isolated from the rest of the mammary gland, although remaining imbedded in its substance? The presence or absence of a main duct appears at first sight to be helpful to our answer to it. But this is not really so, as accessory organs, as we call them, have not invariably got a duct (I need but instance accessory lungs, which are

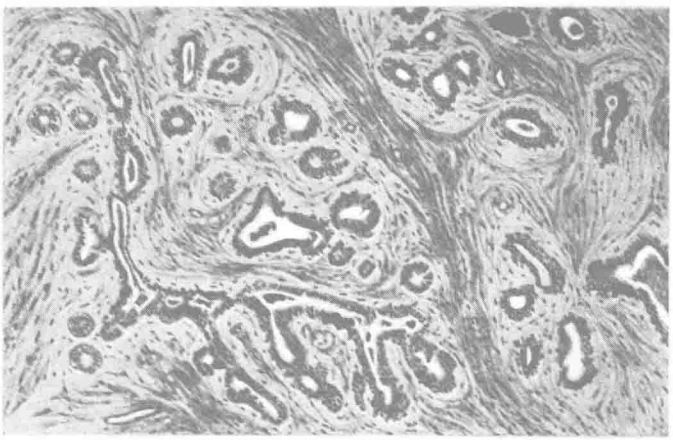

FIG. 3.—Fibro-adenoma of breast. (×90.)

often without a bronchus), whereas many undoubted neoplasms open on the surface of mucous membranes and ducts just like normal glands.

I do not mind confessing the truth at once: I cannot answer the question one way or the other. On looking at this shapeless lump with the naked eye, it would be simple affectation not to call it a tumour. It is only the knowledge of its minute anatomy that raises doubts.

This brings me to the sum and substance of this paper. There are no essential differences, or indeed any differences at all, between tumours and accessory organs, i e., malformations. As Schwalbe (1906) has pointed out, and others before him, there is an unbroken chain, forged of exceedingly fine links, between uni-ovular twins on the one hand, and the simplest tumours on the other. They are all malformations. This is proved by the delicate adaptation of the tissues to each other in many tumours. Of this the present one is an exceedingly good though very unusual instance. But what does it matter how uncommon it is? In the study of tumours, more perhaps than in any other branch of science, it is the exception that proves