A Paper

ON

THE ORIGIN OF TUMOURS *

BY

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I am one of those who have maintained for many years that the secret of tumour formation, which has for so long eluded us, lies somewhere in the study of the normal tissue cells, and that we cannot find the explanation by studying tumour tissue. There have been a great many theories put forward to explain the origin of tumours, but none of them have fulfilled the necessary conditions. Any theory of tumour genesis must be able to explain certain well-established facts. Every fact must fit into the theory, and if it does not then either the fact is wrong and is not admissible, or the theory is false and must be abandoned or modified.

PROPERTIES OF TUMOURS

I shall now briefly state what appear to be established facts about tumours, which any theory of their aetiology will have to explain.

1. Tumour cells grow by their own division and not by converting neighbouring cells into tumour cells.

2. The tumour cell is specific to its original character wherever it may be. Thus the cells of a tumour which started in the rectal epithelium retain the character of rectal epithelium even if they are growing in the liver, in the brain, or in a bone.

3. Tumour cells are species-specific. Thus human tumour cells will not grow in any other animal.

4. Not only are tumours species-specific, but there are a very great many different kinds of tumours for any single species and for each different tissue. We classify tumours according to the tissue in which they originate, but the tumours of the same tissue show great differences. Some grow faster than others, some are more resistant to radium, some tend to degenerate, etc., some to regress, and while some secrete, others do not. It is seldom that two tumours are met with which are really identical in every respect.

5. Tumours can be produced by a great many different agents, such as tar, some aniline dyes, cobalt, sunlight, heat, lime (as in betel-nut chewing), chronic sepsis (as in varicose ulcers of the leg and in septic sinuses), parasites (as in cancer of the stomach produced in rats by *Spiroptera neoplastica*, and in men by the ova of bilharzia), radium and x rays, and the cell-free filtrate which produces the Rous sarcoma. There are, in fact, a very large number of carcinogenetic agents, but there is no common factor between them.

6. Where there is a known cause of tumour formation acting at a certain time there is evidence that a latent period occurs before the appearance of the tumour. This latent period is a very constant factor in the genesis of tumours.

FACTORS INFLUENCING CELL CHANGE

Tumour cells do not differ from normal cells in histological structure, and isolated tumour cells cannot be distinguished from the normal cell of the tissue in which they arose unless their altered relationship to the neighbouring cells, and more particularly to the cells of the connective tissue, can be seen. In fact, tumour cells are normal cells which are behaving abnormally. It is the behaviour of the cell and not its apparent structure that differentiates

it from the normal cell from which it arose. It seems probable that all the cells of the body reproduce themselves at certain times in order to replace cells which have become worn out or old. There is a beautifully exact adjustment to the requirements of the tissue concerned, and it seems certain that every cell in the body is subject to some control as regards its behaviour, and that the chief controlling mechanism resides in the cell itself. It is true that the behaviour of any cell may be profoundly modified by its environment and by factors outside the cell. Hormones from the thyroid, the pituitary, the gonad, the adrenal, and many other glands, affect the behaviour of whole groups of cells. Hormones, or similar substances from other cells, also affect the cell's behaviour, as is seen in the repair of injuries, but the response of the cell to these various factors is fixed, and its behaviour is primarily determined by its own inherent controlling mechanism, which is inherited from the germ cells from which it originally arose. The individual cell is much like a human being: it may be greatly altered by its surroundings, its nourishment, and hosts of other factors, but its inherent character and the way in which it will respond to different factors in the environment is determined by the genes it has inherited from its ancestors. When we find that a cell, or a small group of cells, is behaving in a radically different manner from its neighbours in the same area, we are forced to conclude that some radical change has taken place in the nucleus of the cell.

ANALOGY OF GERM CELL

We can now attempt to visualize the nature of this controlling mechanism which resides within the cell, but in order to do so we must refer to our knowledge of the germ cell in which the behaviour of the cells can be studied most easily. We know from recent biological studies that every human cell contains twenty-four pairs of chromosomes within its nucleus, that each chromosome contains a vast number of genes, and these genes control the behaviour under every possible condition of every cell wherever it may be situated.

When one germ cell unites with another germ cell of the opposite sex to form the fertilized germ cell, which will ultimately become the foetus, this fertilized germ cell will contain in its nucleus a complete double set of twenty-four chromosomes (in the case of man) and a complete set of genes from both the original parent cells. The genes in this cell will control, after differentiation has commenced, what the daughter cells will become in the developing foetus, whether they become muscle cells, nerve cells, bone cells, epithelial cells, or connective tissue cells, and how they will behave, so long as they exist, and will even determine their life cycle.

Now if this is true of the germ cells—and no one disputes it—then it must be equally true of the somatic cell. It seems impossible to argue otherwise. It must not be overlooked that the somatic adult cell also reproduces itself. There are two distinct forms of reproduction of cells: reproduction by fertilized germ cells, and parthenogenesis of ordinary or somatic cells. Individuals develop according to the characters they inherit from their parents, and in the same way the tissue cells develop according to the characters *they* inherit from *their* parents. The parent, or father, of every cell decides the character and behaviour of the daughter cells, and this is just as true of the somatic cells as it is of the germ cells. There are two kinds of inheritance: the inheritance of the germ cell and the inheritance of the somatic cell. In the recognition of this fact lies the explanation of tumours. We know from studies of the germ cells that a change can occur in the nature of the genes of a germ cell from influences in the environment, and therefore extrinsic to the cell itself. Such a change in a gene is

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called a mutation, and when a mutation occurs the gene or genes concerned will continue to breed true to the mutation or change which they have undergone. It is believed by most biologists at the present day that accidental gene mutation has been very largely responsible for the evolution of new species by giving natural selection a chance selectively to protect advantageous mutations.

THEORY OF GENE MUTATION.

If a gene mutation can occur in a germ cell, or a cell which is going to become a germ cell, then it can also occur in a somatic cell, and the consequences, though not the same, will be similar.

Let us attempt to visualize what may happen if an epithelial cell is exposed to some external influence which results in a mutation to some of the genes within its nucleus. Such a cell will, when it next undergoes mitosis, pass on to its daughter cells the mutated genes, and there will be a change in the behaviour of these daughter cells as compared to the parent cell from which they originated. If we suppose that the mutation is a bad one, then the daughter cells will be at a disadvantage, and will probably not survive for long, or will die at once, and the mutation will cease to exist, as happens when a bad mutation takes place in the germ cells. If, on the other hand, the mutation is one which is not necessarily disadvantageous, or which gives some definite advantage to the daughter cells, the mutation will tend to persist during the life of the organism, of which the cells containing the gene mutation form units. Should the gene mutation be one for excessive reproduction—that is to say, reproduction in excess of the normal rate for that particular cell—it is obvious that the daughter cells which will result when that cell next undergoes mitosis will be at a considerable advantage as compared with the other cells around them, and will tend to increase abnormally at the expense of the surrounding cells. In other words, the beginning of a tumour will have resulted. The cells in the mutated colony will be normal cells, except that their rate of reproduction will be faster. This is exactly what a simple adenoma or papilloma of epithelial tissue is found to be.

ITS APPLICATION TO SOMATIC CELLS

It will be argued that no experimental evidence of gene mutation in somatic cells is forthcoming, and that we are not justified in accepting such a theory without experimental proof. Yet there are many phenomena which cannot be investigated by experimental methods. Fortunately Nature is continually doing experiments herself, and if we are sufficiently observant and can correctly interpret the results of her experiments, it is sufficient to establish the truth. Gene mutation in somatic cells cannot be proved by experimental laboratory methods at present.

This theory, or hypothesis, of tumour genesis explains how it is that an apparently normal cell becomes parasitic upon its neighbours. It explains the essential difference between a tumour cell and a normal cell: and if it is correct it must explain *all* the facts with regard to tumours that are known to be true. Any agent that produces a gene mutation in a somatic cell may result in the production of a tumour if the mutation affects the genes so as to increase the normal rate of mitosis. We know from the study of genetics that gene mutation can be produced in many different ways, which have no apparent connexion with each other, and that under natural conditions gene mutations do occur, and have been occurring, throughout the history of life, since they are one of the chief causes of variation in species. Mutations in germ cells have been produced artificially in several different ways. Thus Morgan produced a gene mutation in the fly

Drosophila by heavy doses of x rays, and Mottram produced gene mutation by exposing the flies to the beta rays of radium and by exposing the female *Drosophila* to CO_2 . It is certain that gene mutation can be produced by very many different agents, and if tumour formation is due to mutation of somatic cells, it is understandable why we find such diverse agents with carcinogenetic properties.

Such a theory of tumour genesis explains why tumours grow by division of their cells and not by converting the neighbouring cells with which they are in contact into tumour cells. It is perfectly understandable on this theory, as the mutated cells which form the tumour only differ from the normal cells in that they have an excessive power of growth, but there is no way in which they can convey their power to other cells except by inheritance to their own daughter cells. The intensely specific character of tumours is immediately understandable. A gene mutation must breed true, and a cell containing a gene mutation will breed true to the mutation as long as its genetic life exists. An epithelial cell in the mucous membrane of the intestine, having undergone mutation of its genes to excessive or abnormal rate of growth, becomes in time the parent of a mass of similar epithelial cells which have the power of abnormal growth, and these offspring of the mutated parent cell will become a tumour. The cells composing it will always retain their characters of intestinal epithelium wherever they may be. Their transplantation into the liver, brain, or bones is an accident resulting from their excessive growth, but in no way alters their specific characteristics. Their growth rate and their fate may be profoundly altered by differences in blood supply, in the character of their connective tissue connexions, and other factors resulting from the change in their environment, but they will retain the characters of the parent epithelial cell from which they arose. This theory explains the enormous variety and complexity of tumours which may arise even from the same tissue, and a great variety of tumours is what we should expect, depending upon the particular tissue in the cells of which the mutation occurred, and the particular genes in the nucleus which have mutated.

CRITICAL EXAMINATION OF THEORY

There is a marked hereditary factor in cancer incidence, and breeding experiments have shown that by selective breeding this factor can be greatly increased. Thus in some strains of mice, bred by Loeb, the cancer rate was as high as 90 per cent. of those who reached the cancer age, while in other strains it was zero. These experiments all refer to mammary cancer in the females only. All the breeding experiments on hereditary factors in the aetiology of cancer have shown that the factor which is inherited is not cancer or tumour formation itself, but tumour formation in certain cells of a certain tissue—in Loeb's experiments the mammary tissue of the female mouse. The obvious deduction is that the hereditary factor is an hereditary tendency for the cells of some particular organ or tissue to become tumorous. It does not seem unreasonable to suppose that by selective breeding the cell nuclei of some particular tissue may become more liable to mutation of their genes than the tissues of animals in whom there has been no such selective breeding. It seems certain, if this theory is correct, that mutations of somatic cells which do not concern the reproduction of the cell must also occur, and many diseases besides tumours can probably be explained in this way. Many of the melanotic and keratotic changes in the skin are examples of somatic cell mutation, and it is probable the leukaemias can also be thus explained.

Many people have for a long time thought that the explanation of tumour formation lay somewhere in the biology of the normal tissue cell, but it was not until the

Cancer Conference in London in 1928 that the possibility of a mutation of the nucleus of the somatic cells began to be considered seriously. It was suggested by Loeb, Teutschlaender, Strong, and Mavor, but no definite theory was propounded, as most investigators were more concerned with the pros and cons of the infective theory of Gye. Ten years ago, Theodor Boveri, the zoologist, put forward the theory that cancer is due to abnormal mitosis—tetrapolar mitosis—of the cell nucleus resulting in an abnormal number of chromosomes. He had got the same idea, as he attributed tumour formation to genetic changes in the cell nucleus, but this theory was not generally accepted, because the tumour cell, according to his theory, must have a wrong number of chromosomes. There is considerable evidence that the nucleus of the ordinary tumour cell contains the correct number of chromosomes, and that tetrapolar mitosis is at any rate quite uncommon in tumour cells. The whole subject has been much confused by the fact that tumour cells are often found with all sorts of abnormal nuclear structure, but there is every reason for believing that the ordinary tumour cell is quite normal as regards its chromosomes, and that gene mutation and not multipolar mitosis is the primary factor in tumour genesis. More recently, in 1930, R. J. Ludford gave an excellent résumé of the whole subject, but it did not receive the attention it deserved.

The strongest argument for believing that this theory of tumour genesis is the true one is that it is possible, by means of it, to explain all the different phenomena that have been observed in tumours and their behaviour. No other theory has made it possible to interpret all the observed facts about tumours, and as the facts are seen to fit in and come into line, as it were, the inference becomes very strong that the theory is correct. How it will help in solving the problem of the cure of tumours, which to us as doctors is of more importance, remains to be seen. At first sight it looks as if it will not help at all. But experience in medicine and surgery has taught us that when the cause of a disease is known we are in a fair way to discovering how to prevent or cure it. Cause and effect are a natural sequence, and if we know the cause it cannot but help towards the ultimate goal of full control over this great class of diseases which we call tumours, and which hitherto we have been so comparatively helpless in attacking successfully.

SUMMARY

1. The essential difference between a normal cell and a tumour cell is one of behaviour, not of apparent structure. The tumour cell grows faster than the normal cell.
2. There are two kinds of reproduction—that which produces a new individual, and that which results in the replacements of injured or worn-out cells in our tissues.
3. All cells, both germ cells and somatic cells, breed true to their parent cells, and this breeding is controlled by the genes in their nuclei.
4. Changes or mutations of the genes in the nuclei may occur, and, when they do, the daughter cells will always breed true to the mutation.
5. Tumours are the result of a mutation of the genes controlling division of somatic cells.

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A NOTE ON THE OPERATIVE TREATMENT OF FACIAL PALSY

WITH AN ACCOUNT OF SOME ANIMAL EXPERIMENTS

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The experimental inquiry on which the following notes are based was carried out by Dr. Arthur B. Duel and myself at Laurelwood, Dutchess County, New York State, during the years 1930 and 1931. A full account of the experiments is printed in the *Archives of Oto-Laryngology*, January, 1932.

Each anastomosis operation was combined with the removal of the facial nerve from the aqueduct of Fallopius. Sometimes, on gentle traction on the central end of the divided facial nerve, 3 cm. of the nerve came away. This was followed by escape of cerebro-spinal fluid from the aqueduct. The object in view was to prevent the union of the divided ends of the facial nerve, which would vitiate the clinical results. The stimulation of the facial area of the Rolandic cortex, and of the nerves in the posterior fossa of the base of the skull, was undertaken as

a routine in the final examination of each experimental animal.

The grafting of the hypoglossal, descendens noni, or glosso-pharyngeal nerve to the facial nerve in man is followed, as recovery takes place, by associated movements during eating and swallowing. Whether such movements ever disappear we do not know, but while they last they are disfiguring and distressing to patients during meals. When, in our baboons, one of the above nerves was united to the facial, associated movements were observed during the fourth month from the date of the experiment, and they continued without remission till the animal was killed. When a sensory nerve—for example, auriculo-temporal—was grafted to the facial nerve no associated movements were expected and none were observed. The spinal accessory nerve was not employed in the anastomosis experiments because, in the many cases we had observed in man, the contraction of the muscles of the face was associated with the contraction of the sternomastoid and trapezius muscles. This is a great disability. Further, there is deformity of the neck, and maybe drooping of the shoulder. The contraction of the muscles of the face dissociated from that of the shoulder muscles, the movement most desired, is seldom if ever attained, even many years after operation.