Experimental Production of Malignant Tumours*

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THE investigations of the last thirty years have proved that the cells of the higher vertebrates, under appropriate conditions, are capable of unlimited proliferation, and it is of importance in discussing the problems of experimental carcinogenesis to remember this fact, and to have clear ideas of the characteristic features of the proliferation of new growths, including cancer. This is very necessary because nothing is commoner in the literature of the subject than loose statements that this or that agent confers on the cells powers of unlimited proliferation, which is nonsense, seeing they already possess these powers.

The essential feature is the uncontrolled or autonomous character of the cellular proliferation; that is to say, the agencies which are effective in the body in limiting the rate and amount of growth and cell division are ineffective against true new growths. This is true of both classes of new growths, the benign as well as the malignant. Examples are seen in the fatty tumours, lipomata, which go on increasing in size in an emaciated individual, and the uterine myomata which grow progressively even after the menopause while the ordinary uterine muscle is shrinking or quiescent. The malignant new growths, carcinoma and sarcoma, exhibit this feature still more clearly because many show a more rapid rate of growth.

The other distinctive features of the malignant as contrasted with the benign new growths are differences in degree, rather than in kind, and their more perfect independence or autonomy, manifests itself in infiltrative progress, disorganising and destroying the normal tissues encountered, by pressure from without, or occlusion and rupture of blood supply. The stretching and tearing of the walls of blood and lymph vessels open the way for the entrance of smaller or larger aggregates of the parenchyma cells into the vessels and these, transferred to remote situations, further exhibit their independence and adaptability to new surroundings by the formation of secondary centres of growth, or metastases. It is these manifestations of neoplasia which render cancer so formidable a problem in treatment.

These new proliferative conditions arise in limited localised foci and once they have reached a size sufficient for recognition, further increase takes place only from the descendants of the already transformed cells without fresh accessions from the surrounding elements of the same kind. The original focus may be solitary, or several foci (all minute) may appear almost simultaneously, and soon fuse into one tumour. One type of cell only acquires these new properties and by its multiplication gives rise to the new formation, so that it is usually possible by microscopic examination to infer the tissue of origin, even after the tumour has reached a great size.

The growths of any one tissue do not reproduce the full characters of the differentiated tissue of origin to the same extent. They form a continuous series ranging from apparently perfect reproduction of the histology of the parent tissue to a condition in which no specific differentiation can be recognised at all. Much unnecessary ink has been spilt in devising suitable words to describe this 'undifferentiated', 'dedifferentiated', 'anaplastic' or 'embryonic' state, but what is worth emphasising is the fact that the degree to which it occurs is relatively fixed in any one new growth, and is maintained practically unaltered throughout its course. The rate of growth shows a similar uncorrelated series of gradations and there is much evidence to show that this also is (or at least may be) an initial, inherent, quality of the essential constituent parenchyma cells.

Many of the ideas and conclusions in the preceding summary have obtained a welcome precision and validity from the study of the transplantable malignant new growths of the mouse and rat during the past thirty years. In consequence we may now, with some confidence, define the new growths as single tissue proliferations arising in a localised area, growing from their own resources in an uncontrolled manner, showing a continuous graduated series in those arising from any one tissue, both in histological structure and in rate and habit of growth. In spite of this great range, any one variety is relatively permanent. Descriptive convenience has determined the order in which these characters are enumerated as I find it impossible to give them marks indicating relative importance. We are still without explanation of the process which embraces all these characters and it is hazardous (to me impossible) to accept a hypothesis of the nature and origin of new growths which omits any of them from its ambit.

The necessity, here indicated, of keeping in mind several nearly independent biological processes is common to many pathological problems. It prevents that artificial simplification of the material, which has been so powerful an instrument in the advancement of the physical sciences, and to a considerable extent of physiology.

The attempted solutions of the problem of the nature and causation of malignant new growths, carcinogenesis, may be discussed here in three groups, namely, (1) the genetical hypothesis originating with Boveri, and modified by Bauer; (2) the virus hypothesis particularly associated with the names of Borrel, Rous and Gye; (3) the special form of the chronic irritation theory of Virchow which has arisen on the basis of the work of Yamagiwa on the experimental production of tar cancer.

Boveri's hypothesis was an outcome of his well-

*Opening address at a discussion at the Royal Society on June 15, to appear with other papers contributed to the discussion in *Proc. Roy. Soc.*, B, 113, 268, August 1933.

known studies on the development of dispermfertilised echinoderm eggs. Boveri had shown that the haploid number of chromosomes or any multiple of it was compatible with normal development He ascribed the pathological development of these disperm eggs to chromosome defect, one or more of the four primary blastomeres having received an incomplete set of chromosomes from the multipolar first segmentation division.

Direct observation on cancer cells showed that a constant abnormal chromosome number was not found in any one new growth, and the hypothesis was accordingly modified by assuming an invisible, partial, damage to individual chromosomes. The necessity of assuming a haphazard origin from multipolar mitosis retreated into the background, Boveri's own attempts to initiate malignant new growths by this means having failed. It was an easy step to shift this assumed damage to the genes, the invisible chromosome constituents bearing the hereditary factors. This assumption made the hypothesis practically invulnerable by withdrawing it from the possibility of experimental proof or disproof. The main objection to it now is the necessity involved of assuming a large number of constituent units in each gene, to allow for the great number of slight modifications presented by the new growths of any one tissue, all practically permanent.

The modern discussion of the virus hypothesis revolves around the study of the filterable tumours of the domestic fowl first discovered by Rous. Rous himself described four strains of sarcomata, all transmissible by cell-free filtrates, and many pathologically distinct. Subsequent workers, according to a recent review by Murphy, have brought the number up to thirty. Their most remarkable feature is the biological and histological constancy of the growths propagated by cell-free filtrates and the multiplication of the active constituent of the filtrates, during growth in the susceptible animal. While the latter character points to a living, self-reproducing agent, or virus, the variety of stable strains, each requiring a slightly different virus, has proved too much for many workers, and an enzyme-like derivative of the cell protoplasm has been imagined to surmount this fence.

Gye's genial conception of a factor derived from the host cells and carrying all the specific distinctive characters of the tumour strain, acting in conjunction with a relatively non-specific virus, is still without direct experimental proof. Like the enzyme modification, the greatest obstacle to its acceptance is the failure to demonstrate cell-free transmission in the laboratory strains of mouse and rat tumours. Until this is accomplished, it is dangerous to transfer conceptions arising out of the study of the filterable new growths of the fowl to the elucidation of the nature and causation of the new growths of other animals and man. On the other hand, the similarity in behaviour of the filterable tumours to the new growths of mammals imposes the necessity of investigating them, until the nature of the agent is elucidated and its mode of action, so different from that of the majority of viruses, is explained.

The experimental confirmation of Virchow's chronic irritation theory in the last twenty years, has established its validity as a concise description of the emergence of cancer after prolonged, localised slight irritation of the tissues by a variety of agents, and nothing more. Wide differences of opinion still find expression as to how this result is brought about.

The course of a typical experiment of tar cancer induction in mice is as follows: If 100 mice be painted twice weekly on a small area of the back, the following series of changes are observed. In the first two or three weeks the hair hypertrophies and becomes thicker and longer on the painted area. The hypertrophied hairs then fall out and are not replaced and the tarred area becomes hairless and remains so. If the skin at this stage be examined microscopically, the covering epithelium is found to be thickened, the sub-epithelial tissues show a variable amount of increased cellularity and infiltration with lymphocytes, mast cells, and a few polymorph leucocytes. In the deeper layers, sometimes even below the panniculus carnosus, the tips of hypertrophied hair follicles are found, but these ultimately disappear as painting is continued. After 12–16 weeks, localised thickenings of the squamous epithelium appear as discrete warty prominences in the otherwise smooth skin surface. One or more of these increase in size and project above the surface as warty outgrowths. Microscopically they have the structure of benign papillomata and if painting is now stopped they may either (1) disappear completely, (2) remain as warty papillomata for a long time, slowly increasing in size, or (3) after a variable length of time, begin to grow more rapidly, becoming adherent to the surrounding skin and deeper tissues. Their further progress is continuous and the growths manifest all the features of cancer both to the naked eye and microscopically. The death of the mouse follows in 6–8 weeks and, after death, metastases may be found in the nearest lymph nodes and in the lungs, occasionally in other internal organs. In a certain number of animals, the proliferative condition is malignant from its first appearance, without the apparently benign intermediate stage.

We have not yet any method of distinguishing the papillomata which will remain quiescent from those destined to undergo the further progressive malignant development, and in consequence, during the remainder of the time of observation, more and more of the apparently benign warts pass into the third (malignant) group, until after 12–15 months all the mice have developed tar cancers with the exception of a few which still bear simple warty papillomata and one or two in which no proliferative changes have occurred at all. The same succession of changes follows the intermittent long-continued application of a number of different chemical substances, some related to coal tar, others not.

The processes involved are apparently the same as those responsible for the development of several forms of industrial cancer, and the experimental work has provided a secure basis for the incrimination of tar, shale oil, soot, and arsenic in the causation of the corresponding industrial cancer. In addition, other chemical substances exuded by animal parasites, and physical agencies such as cold, ultra-violet light, X-rays and radium radiation can replace coal tar. The preliminary silent period and successively appearing growths as the applications are continued, are exhibited by the intentional and unintentional experiments alike. They furnish a simple, natural, explanation of the age incidence of cancer, a feature which formerly seemed mysterious.

While the constancy of the results of such experiments and the frequency and restriction of certain cancers to those following definite occupations involving exposure to the same substances fully justify the naming of them as *carcinogenic*, it does not take much reflection to see that the essential nature of cancer and the cellular changes involved remain unexplained. Although the agents are applied uniformly over a considerable area, the cancerous process appears only in localised foci and not diffusely. Even in those cases in which a diffuse origin throughout a whole organ is encountered, it is almost certainly due to close juxtaposition of many minute foci and not to a spreading involvement of adjacent unaffected cells.

The chemical and physical carcinogenic agents, in my opinion, act indirectly; they set up conditions in the tissues such that, as a new departure, here and there cancerous foci are started. The chemical properties of these agents give no indication of how the autonomous, uncontrolled type of proliferation is induced, indeed they are so varied that it is difficult to see how they can give any definite indication of the nature of the cellular mechanism involved. Until this difficulty is at least partially obviated, it seems unnecessary to indulge in the further speculation, that the less precisely known carcinogenic agents, secretions of animal parasites, application of cold, X-rays, etc., produce this effect by liberating in the tissues substances more or less closely related chemically to one or other of the pure substances with carcinogenic action.

From this brief summary it is clear that the experimental induction of malignant growth reproduces perfectly the phenomena which occur in the development of occupational cancer from exposure to tar or X-rays, for example. The other forms of cancer for which no definite irritant can be identified at present are so similar in their mode of occurrence and the length of time necessary for their appearance that it is reasonable to accept the facts of experimental carcinogenesis as a model of the genesis of the others also. An attempt has been made to indicate directions in which difficulties still remain. The definition of these difficulties, and the material and methods by which they are being attacked, we owe to the modern development of experimental carcinogenesis.

Art and Mythology in Asia

IN popular estimation, 'mythology' is a term appropriated to legends and traditions concerning the gods and spiritual beings of religions other than Christianity and its forerunner, the religion of the Hebrews. Such a discrimination is apt to give an entirely wrong impression of the place held by a body of tradition in the life and thought of a people. Yet the term is not without its convenience, provided that it is understood that, in spite of much that in our judgment seems trivial, irreverent or even worse, these traditions stand in the same relation to the religious feelings of the people among whom they are current, as the sacred writings to the emotions of those who profess what are commonly regarded as the higher religions.

It is as understood in this sense that the term has been used in the title "Asiatic Mythology" under which a publication has appeared recently, a translation from the French, which is the result of a collaboration among the members of the staff of the Musée Guimet, that treasure house in Paris of objects illustrative of the religion and art of the Orient*. In this work the religious conceptions of Persia, India, Tibet, Further India, and Indonesia, Central Asia, China and Japan have been reviewed, more particularly in so far as they have been embodied in works of art—paintings and sculpture—not only to present the form and attributes of gods and spirits, but also to depict scenes from their sacred story. The objects which have been chosen for reproduction to illustrate and expand—for this is what they really do—the texts of the distinguished collaborators are mostly taken from the choicer specimens in the museum, though some are from the Louvre, and might in themselves alone afford no inadequate introduction to the religious and artistic concepts of the parts of Asia with which the authors deal.

It is appropriate that this survey of Asiatic mythology should open, after an introduction by M. Paul Louis Couchoud, with a chapter on Persia from Achæmenid times down to and including the Mahommedan period by M. Cl. Huart. As the archæological exploration of the Middle East progresses, it looks more and more as if northern Mesopotamia and the Iranian plateau were a key position for some of the major problems of prehistoric and early historic cultural and racial movement. In later times the lands which we now call Persia, and the adjacent regions to the east

* "Asiatic Mythology: a Detailed Description and Explanation of the Mythologies of all the Great Nations of Asia". By J. Hackin, Clément Huart, Raymonde Linossier, H. de Wilman-Grabowska, Charles-Henri Marchal, Henri Maspero, Serge Eliseev. Translated by F. M. Atkinson. Pp. 460. (London, Bombay and Sydney: George G. Harrap and Co., Ltd., 1932.) 63*s*. net.