BRITISH MEDICAL JOURNAL

LONDON

SATURDAY JUNE 21 1941

DEVELOPMENT OF THE MALIGNANT TUMOUR

Recent studies of the genesis of cancer show that the process is often more gradual than was once thought, and that its real beginnings lie far back in what has usually been regarded as a precancerous period of wholly non-specific hyperplasia. This is seen most clearly from a series of ingenious experiments described in papers from the Rockefeller Institute, one by Rous and Kidd[1] and the other by MacKenzie and Rous[2]; and support is forthcoming from other recent and earlier studies. The Rockefeller workers, using the rabbit's ear, have again investigated the beginnings of tar tumours. They find that if painting is completely discontinued at the end of a month or so, no changes are seen beyond a slight non-specific inflammation, and perhaps here and there the suggestion of an early papilloma. Soon these disturbances subside, and, in the absence of further treatment, the ear will thenceforth remain free of papillomas; yet some of the epithelial cells have already received that special, specific, and irreversible bias which determines that when favourable conditions arise they or their descendants will become cancerous. If within a few weeks or months the painting process is renewed, thus providing the necessary favourable conditions, some of these biased cells now proliferate and form papillomas; this occurs even in areas where no sign of papilloma has previously been found. The abnormal tendency to multiplication and tumour formation shown by the affected cells is still dependent on the continued presence of the tar; if the tar is withdrawn the papillomas steadily dwindle, until ultimately even microscopical examination may fail to reveal any persisting tumour cells. If the tar is applied once more one or several of the papillomas may again appear. The successive disappearance and reappearance of a particular papilloma may be demonstrated in this way, but each time it reappears more promptly and becomes quiescent more slowly. Stroma changes, too, are more persistent. Eventually there is no retrogression even if tarring is completely stopped: the exhibition of the cancerous tendency no longer depends on coexisting favourable conditions, and the cells are obviously malignant.

Not all papillomas follow this course. Many disappear by the way, many appear late, and some pass more directly into the fully cancerous condition. Cells vary among themselves, and at any one time those in different parts of a papilloma may show different degrees of malignancy. Rous and his colleagues are struck, first, by the occurrence of these latent cancerous cells, indistinguishable from normal cells; and, secondly, by the continuity of the transition from these normal-looking cells up to the most malignant. If the tarring goes on indefinitely there is, according to the typical process visualized by Rous and his colleagues, an orderly progression by imperceptible stages. This same feature of gradualness or continuity has impressed Sir Robert Muir in his recent study of the development of human breast cancers.[3] He describes how, in those relatively few cases in which he could be sure of the facts, a single and continuous process is seen. This moves from the simplest recognizable hyperplasia of the epithelial lining of mammary duct or acinus, through various stages of increasing disorder of growth, on to the frankly malignant condition, and thence to the completely unorganized and anaplastic state. In the Shope skin papilloma—a virus disease of rabbits—there is a similar continuous trend from the early benign wart through stages less well organized to evident neoplasia and even, as before, to the completely unorganized state. This gradual transition appears to be characteristic of epithelial cancers in general and possibly of all malignant disease, though it must be recognized that the genesis of sarcomas is difficult to study, and often, even in cancers proper, the intermediate stages seem to be more or less completely telescoped. Thus the view emerges that the point which in practice is taken as the end of the precancerous period does not mark the initiation of some essentially new and novel process in the cell. It is simply the point at which the tendency to cancer has become so strong that it can no longer be overcome by ordinary bodily reaction. This seems the most reasonable explanation of the apparently critical nature of the end-point of the precancerous period. Rous and Kidd, however, take a slightly different view. They insist on the neoplastic nature of cells in the precancerous period, but think that progress towards unmistakable malignancy occurs in a sequence of numerous steps rather than in a truly continuous manner, the step at the end of the precancerous period often being more abrupt than the others and possibly different.

The experiments of Rous, Kidd, and MacKenzie bring the question of latent cancer again into prominence. It is shown, as explained above, that epithelial cells already capable of producing tumours when given the opportunity may lie quiescent for long periods—six months at least. It is shown also that during this time the quiescent cells are exactly like the corresponding normal cells in both behaviour and histological characters. In this quiescent state they display no invasive qualities, and they are entirely subservient to the needs of the body. They may, for instance, take part in a reparative process and, multiplying, may spread over an adjacent injured area to form a new epithelial covering. The latent capacity to form tumours in favourable circumstances is greater in some cases than in others, and the capacity is transmissible to daughter cells. This has not been proved for sarcomas; but we are faced with the possibility—probability, in fact—that scattered here and there throughout the body there are from time to time quiescent cancer cells ready to flare up into malignant tumours under certain conditions. In some such cells, to judge from the tar experiments, the quiescent state may always have existed; in others it may have supervened only after a period of tumour-forming activity. In human beings the great majority of tumours are already malignant when first observed. They are simply those tumours which, by the activity of the carcinogenic process, or owing to favourable conditions, have survived to attain full independence. For every one of these, if the tar experiments can be

[1] *J. exp. Med.*, 1941, **73**, 365.
[2] Ibid., **73**, 391.
[3] *J. Path. Bact.*, 1941, **52**, 155.

taken as a guide, a multitude must have perished by the way, and there may be some cancerous cells still lying inert. Not so very different, perhaps, are those cells which, derived from clinically observed cancers of human beings, remain indolent over a long period. This must be the case, for example, when metastases light up and are noticed years after the primary tumour has been excised.

MacKenzie and Rous stress the need for distinguishing clearly between factors which cause the primary cancerous bias in cells and those which enable biased cells to manifest their carcinogenic capacities. In tar the two factors are combined: tar initiates the cancerous change, and also provides conditions under which fully malignant growths may come into being. But the two factors are not always thus closely associated. It is possible, for instance, that there may be carcinogens which, when acting alone, fail to produce tumours because they cannot fulfil the second function mentioned; but of such carcinogens nothing is known. Of the other possibility—namely, that some factors exist which are capable only of unmasking the cancerous tendency of already biased cells—we know a little more. In the experiments of Rous, Kidd, and MacKenzie it is shown that epithelial cells which have developed an initial cancerous bias before tarring is stopped, and which have afterwards become quiescent, may flare up and become manifestly malignant if painted with turpentine or when involved in the repair tissue of a healing wound. Neither turpentine nor trauma will of itself produce tumours in normal skin. Deelman observed long ago that the repair of wounds in the tarred skin of mice was often accompanied by the appearance of papillomas and carcinomas at the healing edge of the new scar. Clinical pathologists know that bacterial infection may stimulate tumour growth and increase malignancy. Surgeons sometimes observe that excision of cancers from an expanse of irradiated human skin is followed by the development of a wholly new malignant growth in the healing edge of the wound. Injection of Scharlach R into a benign Shope papilloma may delay regressive changes. The factors so far known to favour increase in malignancy seem all to be associated with inflammation and fibroblastic proliferation. Perhaps the factors discussed above are rather different from those which, attributable to the host, may exert an influence even on frankly malignant cells and so play a part in determining the histological picture.[4] More knowledge is needed on this. Information is also required on the opposite set of conditions—that is, on those bodily factors which tend to prevent the latent cancer cell from multiplying and proceeding to tumour formation. Should it be possible to utilize or enhance the action of these factors, then it may be hoped we shall be in a position to tackle even the more malignant of established tumours.

The observation that cancerous cells can lie dormant and then rapidly become malignant as a consequence of traumatic or other stimuli—never before so clearly demonstrated as in these experiments of Rous and his colleagues—has obvious medico-legal significance. They support the belief that trauma—a fracture, for instance—may provide conditions favourable to the rapid appearance of a clinically observable malignant tumour, and thus, in a legal sense, be a cause of tumours.

But with all these discoveries the essential cause of cancer remains elusive. The specific abnormal tendency to cell multiplication is the basic phenomenon and the substrate on which the various accessory factors operate. We still seek for what lies behind this specific change in cellular activity; and, notwithstanding greater histological and biological knowledge of precancerous and later stages, it is still not possible to visualize the state of affairs in the cell itself. The development of a typical or "textbook" example of cancer is now seen as a continuous and single process extending through the precancerous period and into the period of obvious malignancy. If this view is accepted, and it seems it must be, the outstanding feature is the continuity of the process, the smooth transition from one phase to the next. A long and orderly succession of cell mutations such as would give the required apparent continuity is improbable, and a similarly orderly series of consecutive mutations of a virus seems little more probable. In the absence of direct knowledge of the significant intracellular conditions, discussion of this aspect of the cancer problem is unprofitable. But we are now on a different footing in regard to the initiation of cancerous change. Applications of tar to the rabbit skin result in the appearance first of papillomas and then of carcinomas, and the same holds good for the Shope virus. In one sense, then, both tar and virus may be causes of cancer. The remarkable feature of recent studies is that, with widening knowledge of these two rabbit papillomas, the parallel between them becomes more and more close. Thus in both there is the same increasing disorderliness of growth as the fully malignant stage is approached. Even the occurrence of latent cancerous cells seems in no way peculiar to papillomas induced by tar, for papillomas caused by Shope virus occasionally reappear spontaneously at spots where they have once vanished. Evidently the cancerous condition is the same, whether apparently caused by a physical agent or by a virus. The problem of the moment is whether a virus is present in tar tumours (a reasonable question, as Shope virus, though not directly demonstrable, is known to persist indefinitely in transplanted Shope cancers), or whether there is some other unifying principle to be discovered.

[4] *Amer. J. Cancer*, 1940, **39**, 1.

THE EFFECT OF MALARIA ON THE BIRTH RATE

The dominant part played by malaria as a cause of mortality in tropical and subtropical countries is often stressed. It is not so commonly recognized how difficult it is to determine, even approximately, what is the actual mortality due to malaria. One reason for this difficulty is that malarial mortality in indigenous populations of tropical countries is mainly displayed as raised infantile mortality. Hence statistics rarely help us, for a raised infantile mortality is obviously very difficult to analyse into its components. The effect of malaria is not, however, confined to post-natal mortality, for death of the foetus in the form of stillbirths and abortions is a pronounced feature of this disease, and here statistics very rarely give us any information. It is, however, very generally assumed that these antenatal effects, coupled very probably with reduced conceptions, are displayed in a lowered birth rate which is supposed to exist under malarious conditions in a complementary manner to the raised death rate. Nevertheless a number of observers investigating malaria in such circumstances have recorded their opinion that