will be the difficulty in its reverting to an ancestral type. Thus one sees that, with certain exceptions, nerve cells, having once been formed, are incapable of multiplication and in fact just as nerve, muscle, connective tissue, and epithelium may be said to form a descending scale in respect to their specialization or departure from the ancestral type, so do these various tissues differ in their attributes and in their powers of multiplication from the ancestral cell. The epithelial cells may, indeed, be looked upon as those cells which have been left over after the more specialized cells have been budded off, and it follows that it is these cells which will most nearly resemble the ancestral cells in their attributes, and especially in their powers of reproduction, and will most easily revert to the original type. In other words, as this reversion must be in the form of a degeneration, it is in these cells that one may expect a degenerative reversion most readily to occur. It may be objected that the reversion ought to be to an embryonic type, that is to say, to a type which is capable of reproducing the whole organism; but, in the higher animals at least, the power of so complete a reversion has been lost, though in many of the lower animals, and in most of the higher plants, this capacity is retained by the least specialized of the individual cells of which the organism is composed.

If, then, the tendency of degenerating epithelial cells to a reversion to a germinal type be allowed, the next thing to consider is, what the causes are which determine the appearance of the disease at any one time or place. With regard to time, the essential condition is that the epithelial cells should be becoming somewhat inert, that is to say, growing prematurely old, and losing their normal powers of reproduction or multiplication. In other words, that, with regard to them, the decadent period of life should have set in. It has often been said that a man is as old as his vessels, and this is equally true of most of the organs of the body, and of the epithelial cells more especially. A tendency to what may be described as precocious degeneration of the epithelium may be a parental legacy; and just as in some families the vessels tend to develop atheroma early, whilst in others the hair becomes prematurely white or thin, or the nerve cells all soon tend to undergo atrophy, so also with these tissues the liability to the early formation of cancer is not infrequently a pronounced family characteristic. Again, the favourite sites for cancer are those, like the breast or the cervix uteri, where degenerative processes appear most early. Further, with the increased rapidity of living under modern conditions, all the degenerative diseases are tending to increase in frequency, and to appear at earlier ages than was the case with our more slow-living ancestors. I need only instance general paralysis of the insane and degenerative conditions of the heart muscle apart from valvular disease.

Again, with regard to cancer houses, streets, and villages, any external conditions which favour the early onset of degenerative changes in epithelial structures will favour the development of cancer, hence it is not surprising that environment should be effective within somewhat narrow limits in determining the frequency of the disease. The high percentage of stomach cases is further hardly to be wondered at considering the amount of irritation to which this organ is exposed by overcooked, hard, irritating food on the one hand, and nauseous, artificially, semi-digested messes on the other, let alone the worry it suffers from the continous drugging it receives on the wall-poster advice of the quack medicine vendor. It is therefore small cause for surprise that the stomach epithelium tends early to grow old and feeble, and the cells individually to strive to retrace their evolutionary history.

So far, then, if I have succeeded in establishing that under certain conditions the epithelial tissues, and especially those in certain regions, are in a state ripe, as it were, for reverting to an ancestral germinal type, then it only needs that some exciting cause should appear in order to start the cancerous growth. But even if started, if it is to go on, the nourishment must be abundant, and hence, again, the great liability to cancer of those regions, like the breast and the uterus, where the mechanical arrangements for the supply of blood are far in excess of the needs of a decaying or degenerating organ. The exciting cause may be a mechanical irritant such as a rough tooth or a gall stone, a chemical irritant as occurs when an irritating discharge flows over a granular surface, or a biochemical one as in the case of a simple ulcer becoming malignant, or as in Paget's disease of the nipple. The effect of the exciting cause is probably complex, in that it not only may act as an irritant to the cells, but will also cause dilata-

tion of vessels and excessive blood supply to the part concerned. Thus it seems to me that all the conditions present in cases of cancer can be more readily and satisfactorily explained by this theory than by any other which has so far been advanced.

STRUCTURAL LINKS IN MALIGNANT GROWTHS.

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It is said that the qualities which constitute malignancy differ in degree rather than in kind from the characteristics of benign growths. Thus, for example, simple adenoma becomes malignant adenoma, fibroma becomes sarcoma, and papilloma becomes carcinoma. Again, it is impossible by clinical or pathological methods to distinguish sharply between certain cases of retained placenta, simple and malignant moles, chorion-epithelioma (deciduoma malignum) and even teratoma. Progressive growth and the formation of metastases, the infiltration of surrounding tissues, their atypical character, and the absence of specific symptoms are most frequently noted in carcinoma and sarcoma. The laws which govern the growth of tumours and the "fecundity" of the cellular constituents are as yet unknown, but a rapid rate of multiplication and also of degeneration—in other words, cellular instability—is usual. The growth is not in proportion to the nutrition of the body as a whole or in part, or to the age of the patient—for example, the "cancer age" is late middle life.

In carcinoma both lymphatics and blood vessels are the channels for the supply of nourishment, but in sarcoma no lymphatics are known. In both cases the cells are bathed in nutrient fluid and must be fed by a process of osmosis, perhaps aided by increase of assimilatory activity. The purpose of new growths is, of course, unknown. A parallel is perhaps suggested between cancerous growths and the rank vegetative activity often observed in herbaceous plants and in the larger fungi.

Various irregularities in the divisions of the nucleus have been observed in malignant growths—for example, multipolar spindles, increase in the number of chromosomes or in the amount of stainable substance (chromatin) in the nucleus, direct or simple division, etc. Professor Farmer and his colleagues have recently shown that heterotype nuclear divisions, characterized by a reduced number of chromosomes which are annular or "bunched" in appearance, are attached to the long axis of the spindle, and divide transversely, are present in malignant growths in man. Drs. E. F. Bashford and J. A. Murray have reported the same in other mammals and in fishes.

During the study of a large number of sections made by one of us (F. B.) it was noted that the mitoses were very readily observed in a glandular carcinoma of the rectum, less so in a sarcoma, and least in a scirrhus mammae. The appearance of the mitotic figures, as sketched from microscopical preparations with high magnification, is of interest to all pathologists, and the difference between the slender V-shaped somatic chromosomes and the thick irregularly-shaped heterotypic ones, is especially well shown in Fig. 1. In Fig. 2 the somatic mitosis shown in A stands in sharp contrast with the heterotypic ones, B to G; these sketches are all from a glandular carcinoma of the rectum, and were made with uniform magnification. A similar contrast is shown in the sketches H (somatic) and I (heterotypic), which are from a sarcoma. It was observed that the cells undergoing heterotypic mitosis were frequently enlarged and of a spherical or ovoid form. Another feature noticed in the glandular carcinoma was the occurrence of both somatic and heterotypic mitoses in the glands of Lieberkühn adjacent to the growth, and their tendency to be situated nearer to the lumen than to the basement membrane.

Observations are being made with a view to mapping out the topography of cancer cells by this method and to ascertaining their distribution, as described by Professor Farmer, in various growths and in "heterologous" neoplasms. No evidence was obtained of conjugation of resting nuclei, or of conjugation of cells in pairs ("gametes"), or of appearances resembling the formation of "swarm-spores."

The question arises whether cells which have undergone a reducing nuclear division are "inclined" in plants or in animals to self-fertilization or fertilization from chemical stimuli. Such a phenomenon in cancer would presuppose that a sexual change is signified by this reducing division, similar to the sexual and asexual phases in the life-cycle of certain sporozoa and dependent on intrinsic and extrinsic (environment) forces. Parthenogenesis brought about in some way might explain by reinforcement the wonderful power of mimicry of original structures seen in metastases. It has long been known that parthenogenesis occurs in certain animals, and it has been shown in some cases to result from the lack of separation from the egg-nucleus of the second polar body, or to follow on the re-fusion of this body with the egg-nucleus. As stated by Professor Farmer in his kind reply to my letter of inquiry¹ parthenogenesis has been shown to occur in consequence of chemical stimuli, in cases where the egg-nucleus evidently possesses the reduced number of chromosomes. On the other hand, Dr. Bashford believes that the heterotypic mitoses are the expression of a terminal phase in the life-cycle of the cancer-cell.

Fig. 1.—Part of a section of a glandular carcinoma of the rectum, showing a somatic and heterotypic mitosis in two cells of a gland. Both figures show the "metaphase" stage, the figure being viewed from one of the two poles of the spindle. In the somatic figure nearly the whole of the thirty-two chromosomes are shown; in the heterotypic figure nine thick curved chromosomes are seen in the section.

A second structural change that links malignant processes is afforded by the morphological transition of cells of sarcomatous to those of epithelial form. Many sections of an "adenocysto-sarcoma" of the breast (removed by Mr. C. Whipple at the South Devon Hospital from a woman, aged 52) show that the columnar cells of the intracystic growths pass by gradual transition into large sarcomatous elements. Again, in a huge diffuse melanotic sarcoma of the liver (in another woman, aged 52, under the care of Mr. W. L. Woollcombe), the hepatic capillaries were stuffed with pigmented cells, varying from the size of small endothelial to that of large sarcomatous elements. A pigmented mole over the seventh right intercostal space showed similar pigmented cells in the cutis; the thyroid gland in this case was the seat of an adenoma. Though such a mole may be considered to be sarcomatous or again to be epitheliomatous, I regard it as a primary endothelial tumour, on the same grounds that Raymond Johnson and Lawrence regard "parotid tumours" as endotheliomata.

Similarly, H. D. Rolleston and O. Grünbaum note as follows in a "perithelioma" of the cheek: "Striking features are the transition from cells of a sarcomatous type to cells resembling columnar epithelium and the villous or papillomatous arrangement," despite the use of selective epithelial

stain.² This is not "metaplasia," defined by S. G. Shattock and C. A. Ballance as the transformation of one normal tissue to another, but is akin to true "heterology" (Virchow). It appears to be the reverse of that which is seen in those tumours in which epithelial and sarcomatous elements are formed from "indifferent" tissue.³

Not only may such changes as calcification, pigmentation, vascularity, etc., be faithfully transmitted from primary to secondary growths, but pigment appears in the neighbourhood of certain pigmented secondary deposits (for example, in or between the liver cells). This cannot be explained by the wandering of pigmented sarcoma cells, comparable to the wandering of pigment cells in fishes, but may be an excretion. It even appears in some sections as if the cells of a secondary deposit and those of the organ exert mutual action on each other's shape. Again, carcinoma can convert adjacent normal tissues to stroma. Both phenomena suggest that environment does influence the "germinal" cells of these growths, chemically or otherwise, despite the tendency of Jensen's experiments to magnify the potentiality for growth and reproduction inherent in "epitheliomatous" cells in the mouse.

Fig. 2.—A to G are from the same series of sections as Fig. 1 (glandular carcinoma of rectum). A is a somatic mitosis, metaphase, and 25 of the 32 chromosomes are seen; in B, C and D, the spindle is cut longitudinally; in E, F and G it is cut transversely at about the middle. In B to G the mitoses shown are of the heterotypic kind, the chromosomes being few, thick, and irregularly shaped. In some cases they are evidently ring-shaped, and in E one of the chromosomes shown is branched, being Y-shaped in section. G is probably a multipolar mitosis, the chromosomes showing a tendency to form three groups, but the spindle-threads were not distinct. H and I are from a sarcoma in fascia of thigh, H being a beautiful example of a somatic mitosis, whilst I is heterotypic, the section showing only 4 curved chromosomes. J is from a carcinoma mammae, heterotypic metaphase, showing four thick bent chromosomes; above is seen the resting nucleus of an adjacent cell. The drawings were made with uniform high magnification.

The figures which accompany this paper are from cases under the care of Messrs. R. H. Lucy, W. L. Woollcombe, and C. E. Russel Rendle at the South Devon Hospital, to whom I express my thanks for the material obtained on removal during operations. I am greatly indebted to Mr. F. Cavers for his beautiful and exact drawings, some of which are here reproduced.

REFERENCES.

- ¹ *Nature*, February 25th, 1904, p. 392. ² *Trans. Pathol. Soc. Lond.*, vol. liv, p. 353. ³ The "blastomata" of C. P. White, *Lancet*, February 15th, 1902; and of H. Snow.

THE TREATMENT OF INEBRIETY BY ATROPINE.

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As doubt is sometimes thrown on the efficacy of all short-term systems of treating inebriety, a few notes on the subject based upon a lengthy and somewhat wide experience, may be of interest, especially as I have come to the conclusion that in the majority of cases long periods of detention are wholly unnecessary, and that a complete recovery, with absence of all craving for stimulants, may generally be expected after a course of treatment lasting six weeks.

The advantages of a short-term system, if efficient, are so obvious as not to call for enumeration. The question, of course, is whether the treatment results in permanen