deaf, the imbecile and the mentally defective. For these cases London and the other large towns have special schools, both residential and day. They also have special schools or classes for tuberculous, paralysed, and other crippled children, who are taken there in a special ambulance carriage. Special open-air schools are also provided in the London suburbs, to which anæmic and ill-nourished children are sent for a season. For the defectives, in county areas reliance has usually to be put on residential schools belonging to private charities, to whi h the education authorities subscribe for so many beds. Many authorities now have, or are building, their own homes for the mentally defective and for the epileptic, who, however, must be educated in separate institutions from one another. The parents' consent is necessary, and a weekly parental contribution, where means will allow, is usually required.

For the treatment of curable defects the authority is allowed, subject to the sanction of the Board of Education, but is not obliged, to undertake treatment. The following are the alternatives:—

1. *School clinics*, or out-patient hospitals, established for the purpose. Eleven of these were sanctioned for the year 1909–10, including the purely dental clinic at Cambridge. For dental work there is need of some such institution. But merely for the treatment of skin and eye diseases and of adenoids it is difficult to justify such an establishment, if it is to be decently equipped and arranged. Occasionally, as at Hampstead, Wandsworth, and Norwood, such a clinic is provided by the medical profession in the locality, who together contract with the authority to staff and maintain it.

2. *Use of existing hospitals*, either voluntary or in return for a subsidy. London has such arrangements with three voluntary and 14 subsidised hospitals, adequate payment being made for the clinical assistants and for all expenses incurred. This arrangement is not generally approved by the medical profession, as it increases hospital practice and the privileged practice of the staff; it is not wholly satisfactory to the County Council, as the hospitals stipulate for complete freedom of action. Nevertheless, where the hospital almoners play their part well and refuse treatment to children whose parents can pay, the advantages of this method for the time being are obvious.

3. *Recognised surgeries* are proposed by the British Medical Association for county areas, in which a scale of fees would be payable to most medical men in these areas, after official appointment, for treatment of defects in their surgeries.

4. *School nurses only.*—In contrast to other suggestions the authority may decline to establish a new scheme of treatment. Parents should secure treatment, they may say, under present conditions at the hands of medical practitioners or charitable hospitals, the Poor-law having provided for medical treatment out of the rates for those who cannot afford payment. All that is then necessary is a system of nursing to persuade the parents of what is necessary and to see that it is carried out. In county districts, at least, this should be effected by a subsidy to local nursing associations for the employment of the existing village nurses, preferably through the medium of a county nursing association, which can supply the supervision and instruction necessary. Coördination of nursing in a single system for each county is thus also promoted.

This last system of coping with the physical defects of school-life is certainly at present inadequate. The Poor-law has not yet provided out-patient departments for this kind of work. But reform of the State medical services is at hand, and rather than create new institutions it is best for us to make the utmost use of existing institutions, and so show the need, in reforming the Poor-law or developing the system of State insurance, of creating machinery to deal with these cases of minor ailment in school children as an essential duty of a comprehensive and unified State medical service.

I hope, gentlemen, you will throw yourselves into this school work with zest. It is a fundamental factor in the public health and offers a prospect of immense benefit to national prosperity and happiness, which are primarily dependent on the national health, especially in the rising generation, and especially, therefore, in the public elementary schools.

ON CANCER.

CANCER REGARDED AS AN ADAPTIVE RESPONSE ON THE PART OF CERTAIN CELLS OR CELL GROUPS TO ENVIRONMENTAL CHANGE, AND AS THE RESULT OF A PROCESS OF VARIATION AND SELECTION OF AN "INTER-" OR "INTRA-" CELLULAR KIND.

BY C. J. BOND, F.R.C.S. ENG.,
SENIOR SURGEON TO THE LEICESTER INFIRMARY.

THE object of the following inquiry is to analyse, as far as they are known, the conditions under which the new cell characters which we associate with cancer arise in somatic cells; to inquire whether the three conditions which accompany variation and selection among other organisms are also concerned in the evolution of cancer. These are: (1) struggle for existence among cells; (2) cell proliferation; and (3) cell destruction.

We must start with the fundamental truth that every adaptive response made by cells to environmental change is the outcome of the interaction of two factors—environmental stimulus on the one hand and cell potentiality on the other. The response may be "direct"—that is to say, the conditions under which the reaction occurs may be comparatively simple, and the new cell character may arise in direct response to the changed conditions. Or the conditions of the response may be so complex as to elude analysis, and the new characters may appear to arise just as the so-called spontaneous variations arise in germ cells without any direct reference to the environmental change. In both cases alike, however—in the "direct" form of use acquirement and in the "indirect" form of innate variation—the process is essentially the same. It is one of variation and selection among individual units exposed to changed conditions. These units may be individual cells or they may be represented by the physiologically differentiated parts which compose the cells. In the one case selection will be on an *inter*-cellular, in the other on an *intra*-cellular plane.

Any consideration of the cancer problem must therefore include a consideration of the conditions under which certain cells (as the result of the interaction of environmental stimulus with cell potentiality) exhibit certain characters which enable them to live and multiply more freely under changed surroundings. In this sense, therefore, cancer may be regarded as an adaptive response, and it becomes important to ascertain the conditions under which the response is made.

If we recall the different varieties of cells which together form the individual soma of any multi-cellular organism belonging to one of the higher types, we shall recognise that, from the point of view of cell environment, they may be divided into two great groups: The connective tissue or hylic group (Adami) on the one hand, and the epithelial or lepidic group (Adami) on the other; or from the "adaptation" point of view the group without, and the group with external world relationships. As regards the individual cells of the first or hylic group the cell environment is a dual one; it is made up of the nutrient medium and the activities of neighbouring cells, and in a remoter degree of all the remaining cells which compose the organism. But for the epithelial cell the environment is a threefold one. In addition to the nutrient medium and the activities of neighbouring cells, it embraces also the stimuli of the external world or that portion of it with which the cell is brought into more immediate relationship.

Even those cell aggregates which, by downgrowth or outgrowth from the surface layers, form the glandular organs, although they have lost touch with many external stimuli, they still remain in potential or actual communication with the outside world. For even in their case the mucous channels, the ducts by which their secretions reach the surfaces of the body, serve as channels of communication between these cells and the exterior, and the temporary stasis of contents which frequently and intermittently occurs in these ducts, associated as it is with backward mucous currents, acquires additional importance from our present point of view.[1] The internal secretion of the ductless glands like the thyroid is in reality an external secretion retained under pressure and

[1] Address in Surgery, Bond, THE LANCET, July 29th, 1905, p. 275.

re-absorbed, and is associated with a primary origin of these glands from the epithelial or lepidic cell group having external world relationships.

The endothelial and mesothelial cells, connecting as they do the hylic with the lepidic group, stand in an intermediate position. They line the blood-containing and the lymph-containing spaces and body cavities, and their environment comprises the nutrient medium, blood or lymph, the activities of neighbouring and other cells, and such external influences as reach them from the outside world in the shape of food material, micro-organisms, and chemical substances contained in the blood or lymph streams.

The germ cells form another group having peculiar environmental relations. By virtue of their normal capacity for migration and their abnormal liability to prenatal displacement at different periods of their life-history they establish relations with different kinds of body cells, with body cavities, and with the outside world, and, like the somatic cells of different types among which they grow, they give rise to tumours of a special kind, the teratomata, which include also malignant and benign types.

Thus we can divide the body cells, and the blastomata which spring from them, into two large groups: those in which the external world forms an actual or potential factor in the cell environment, and those in which the environment is limited to the nutrient medium bathing the cells, and the activities of neighbouring cells and those which compose the rest of organism. The latter factor will, of course, be reversed in the two groups. In the case of the epithelial cell it will primarily consist of mesoblastic cells, and in the connective tissue group it will consist of epithelial cells or mesoblastic cells of another subtype.

In thus classifying cells and the new growths which arise from them according to their environmental relationships we must remember that only the ordinary environmental factors normal to the cell in each case are thus included. Under abnormal conditions many outside influences may affect the cells of both groups, both those normally exposed to, and those normally excluded from, contact with the exterior of the body. For instance, wounds, solutions of continuity of surface of all kinds, allow contact with, and the entrance of, foreign substances in the shape of micro-organisms and their secretions. The physical stimuli of light, heat, sound, contact, X ray vibrations, radio-active substances, all these and many other agencies may, under special circumstances, bring about environmental changes and exercise an influence on all kinds of body cells.

Bearing these facts in mind, we are now in a position to examine the conditions under which, as far as they are known, the cells of both groups originate those new characters which are associated with tumour formation, malignant and benign. It is evident that any attempt to explain the cancer problem, as an adaptive reaction if it is to be satisfactory, and any attempt to classify the diversified types of blastomata, if it is to be complete, must include a detailed description of the effect of every environmental factor in relation to each normal and abnormal cell potentiality, hereditary and acquired, in the cell group in which the new characters arise. Such a proceeding is manifestly impossible. But this fact does not render useless a partial analysis of the conditions under which cancer occurs in one—for instance, the epithelial—group of cells. Such an inquiry if conducted on sound principles may throw light on the larger problem.

Following out this conception of the threefold nature of the environment of the normal epithelial cell, the cancer problem will mean for us a consideration of the conditions under which the cancer characters arise in epithelial cells in response to some change in one or all of these three environmental factors. Moreover, a careful study of the differences which distinguish the cancerous from the normal epithelial cell shows that these differences can also be grouped in relation to these same three environmental factors.

I. *Nutritional Factor.*

Let us take the nutritional factor first. The epithelial cancer cell exhibits a greater capacity for absorbing and assimilating nutrient material than the normal epithelial cell Not only so, but in proportion as the normal cell approximates to the cancer type, in such proportion it acquires a larger cytoplasmic surface area capable of assimilating nutrient material. This fact will become apparent when we remember that the fully grown functionally active epithelial cell which covers the skin surface, or lines a mucous cavity, or gland acinus, or gland duct, presents a free cytoplasmic surface to the exterior. It is by this surface that the external secretion which it elaborates reaches the exterior. This surface is not available for the assimilation of nourishment from the blood or lymph stream. It is only available for the ingestion of such nutrient material or foreign substances as may reach the cell from the outside world.

Now in proportion as the cancer cell grows away from its normal relationship to the external world, in proportion as it tends to lead an independent existence, and to grow and multiply amongst the neighbouring mesoblastic cells, in proportion, moreover, as it ceases to pour out external secretion and to carry on normal functions, in such proportion it ceases to exhibit the normal differentiation of cytoplasmic substance into absorbing and secreting surfaces, and develops assimilative and absorbing capacities over its whole cell surface. Moreover, as we should expect, this retrogressive change is most marked in the peripherally placed cells of primary and the cells of secondary growths.

This disturbance of the normal relationship between secreting and absorbing surfaces is characteristic of cancer of the epithelial type, but, as we shall see later, it is not characteristic of cancer of the connective-tissue type. This is probably due to the fact that the normal connective-tissue cell has no external world factor in its environment, consequently the blastomata which originate from these cells do not exhibit changes in reference to it, while coincidently with this distinction we find, also, that external stimuli are more closely associated with the origin of cancer than with the origin of sarcoma.

It is interesting to note that cancers of the breast of the colloid type present only a slight degree of malignancy, and the question arises whether the low degree of malignancy may not be associated with the retention on the part of the epithelial cells which form such growths of some capacity of forming an external secretion which, under the conditions of retention present, brings about the degeneration of the cells.

But whatever may be the nature of the secretory change which distinguishes the cancer from the normal epithelial cell, it is certain that a greatly increased capacity for vegetative growth is one of the distinguishing features of the cancer cell. Vegetative growth means increased assimilation of nourishment, and this in the large epithelial cancer cell means increase in area of cytoplasmic surface capable of assimilation. Moreover, the rapidly recurring cell division characteristic of the cancer cell is closely associated with this recurring alteration of relationship between bulk of cell substance and area of assimilating surface.

There are certain facts which suggest that this increased assimilative capacity in the cancer cell is a further development of a capacity possessed in lesser degree by the normal epithelial cell. Thus, Fischer found that the subcutaneous injection of Scharlach R in olive oil beneath the corium of the rabbit's ear stimulated the epithelial cells of the epidermis, and produced in them a downward growth in the direction of the substance so injected. This experiment demonstrates the influence of an environmental change of a nutritional kind in initiating an adaptive response on the part of epithelial cells exposed to it. In this case the chemiotactic capacity displayed lies within the normal limits of epithelial cell potentiality, while in the case of the cancer cell it extends beyond these limits.

II. *Neighbouring Cell Factor.*

We must now consider the second factor in the environment of the epithelial cell: the physical and chemical activities of the neighbouring cells and of the cells which compose the organism. In response to this "other cell" influence the epithelial cancer cell exhibits capacities of an adaptive kind, of a kind which favours its own vegetative growth and cell division at the expense of the growth and functional activity of the neighbouring cells of different type. The aim (if we may so express it) of the epithelial cancer cell is to stimulate the surrounding mesoblastic cells to a reactionary growth, sufficiently active to provide the necessary vascular support, but not so active or so fully organised as to threaten by fibrous encapsulation the nutrition of the cancer cells. This growth relationship between cell-groups of different structural and functional types (which in normal

development is so delicately balanced) is disturbed by the great vegetative activity of the cancer cell.

As I suggested[2] in 1886, the capsule of any glandular epithelial organ may be regarded as the expression of a reactionary growth on the part of mesoblastic cells to the encroachments made upon them by the growth of cells or cell-groups of a different germ layer origin. The growth limit of any glandular organ is determined, within certain hereditary limits, by the opposition offered by neighbouring mesoblastic cells to the growth of the epithelial cells which compose the organ. The capsule is the result of this adaptive reaction on the part of the mesoblast cells, and the exact stage in ontological development at which a supporting and nourishing stroma becomes a limiting fibrous capsule is a matter of mutual adjustment between the hereditary capacity of epithelial cell growth and division, and the hereditary capacity of connective-tissue cell growth and division. It is only in some such process of mutual adjustment between the activities of cell-groups of different types that we can conceive of the orderly development of the organs and tissues of the multicellular organism as rendered possible.

We may extend this conception of the relationship between supporting stroma and enveloping capsule to the problem of the growth of neoplasms, malignant and benign. The growth of a benign tumour of the lepidic and hylic type is limited by a fibrous investment of connective-tissue growth analogous to the capsule of a normal organ. It is formed by the surrounding cells of different type or sub-type. In this case, also, the stroma, which serves as a support and nourishing medium for the cells of the tumour, becomes at its surface a more fully developed fibrous capsule. The cells of the definitely benign growth exercise the activities of normal tissue cells of corresponding type towards the surrounding mesoblast cells, and the reaction made by the mesoblast cells resembles that made to normal tissue cells.

It is very different with the cells of the malignant growth. The balance of mutual growth resistance has been disturbed. Having lost the capacity for normal cell division, conformable with the exercise of normal function, and the interests of the surrounding tissues and the body as a whole, the cancer cell has gained power to undergo cell division irrespective of the interests of the surrounding tissues and the body as a whole, and conformable only with the fullest exercise of its own vegetative activity. And this adaptive process requires the exercise of a very delicate influence on the part of a cancer cell over the growth activities of the surrounding mesoblast cells. Stimulation above or below the right level results in the development of a limiting and protective capsule on the one hand, or an inadequate nutritive stroma formation on the other. Further, the exercise of this specific influence by the cancer cell induces in the mesoblast cells abnormal growth along the same direction as that in which the cancer cell has itself varied away from the normal epithelial cell. And this result is brought about probably by a bio-chemical rather than by any sperm-like influence on the part of the cancer cell.

The process of stroma formation is a lowly organised phase of the same process of cell division and cell organisation by which, when carried to a higher level of tissue development, the mesoblast cells are enabled to resist the encroaching growth of the cancer cells. Thus Ehrlich and Bashford have shown that under certain conditions of repeated transplantation, the epithelial cells of mouse cancer may evolve a capacity to influence the reactionary growth of the mesoblast cells and reduce it to even a lower level of tissue development. These observers have found that under such conditions the portion of mammary cancer so transplanted may induce in the connective tissue in which it is embedded a low-grade growth indistinguishable histologically from sarcoma. These facts confirm the suggestion that the capacity of the epithelial cancer cell to influence the growth of mesoblastic cells in abnormal directions is an excess variation of a capacity normally possessed in a lesser degree by epithelial cells.

III. *External World Factor.*

We may now consider the third or external world factor in the epithelial cell environment, and try to ascertain in what way, in regard to it, the cancer cell has varied away from the normal epithelial cell.

The two chief adaptations exhibited by epithelial and gland cells in relation to external world stimuli are (1) elaboration of external secretions and (2) deposition of formed material of a protective kind. The epithelial cancer cell shows a diminished capacity for the elaboration and discharge of the secretions formed by normal cells of the type to which it belongs. This peculiarity, as in the case of other cancer characters, is a relative change. Thus the cells of malignant adenomata secrete some mucus. Müller long ago detected casein in the cells of mammary cancer; Waring has found pepsin in gastric, and trypsin in pancreatic cancer tumours. Other observers have detected bile in the metastatic growths formed by liver cancer.

Allowing, however, for these observations, the fact remains that the external secretions elaborated by cancer cells differ quantitatively and qualitatively from the secretions formed by normal epithelial cells of a corresponding type. In fact, the degree to which the cancer cell has lost the power to elaborate normal external secretion is a direct index of its malignancy, and with this decreased capacity in one direction goes increased capacity for vegetative growth, and the point that I particularly wish to emphasise is the desirability of considering this peculiar loss of functional capacity in relation with the special factor in the environment (the external stimuli) with which it is under normal conditions associated.

But besides elaborating external secretions, epithelial surface cells react to the influences of the external world in another way, and that is by the formation and deposition, either within the limits of the growing cell or outside these limits, of material of a protective kind. Thus the surface cells of epidermal tissues undergo keratinous change. And other examples of cytoplasmic differentiation of a similar kind could be mentioned. Now the cells of a squamous-celled epithelioma do not present the same degree of keratinisation as that shown by normal squamous epithelial cells. This is especially noticeable in the cells composing the secondary deposits formed by squamous epithelioma. Neither do such cells present the regular cogwheel interdigitations found in normal cells. It would be interesting to know whether cilia are present in cancer cells arising in ciliated epithelium, and, if so, whether they are found in the cells forming the metastatic deposits found in such tumours.

We may recapitulate this enumeration of the adaptive characters shown by epithelial cancer cells to the three primary factors of epithelial cell environment by saying that the characters associated with the cancer habit indicate diminished or defective adaptation to the external world factor, and increased adaptation to the nutritional factor, and to the activities of other cells. A fully developed and functionally active epithelial cell flourishes with one cell surface attached to the underlying cells and bathed with nutrient lymph, while the other surface is free and exposed to external influences, whereas the epithelial cancer cell grows best with all its surfaces brought into relationship with the activities of neighbouring cells, and bathed in nutrient material of a lymph-like nature. Such, then, is the cancer process viewed as an adaptive response on the part of epithelial cancer cells.

Effect of Bodily Conditions.

Let us now consider epithelial cancer from the standpoint of the individual organism and consider the bodily conditions which are supposed to favour its origin.

Age of individual.—Individual age on closer analysis means relative senility of the different epithelial tissues of different types in the same individual. Cancer tends to originate in epithelial tissues that are growing old. But age means physiologically, number of previous generations passed through by the cells composing the particular tissue in question. And tissues which are nearing, or have reached, the hereditary limit of capacity for normal function and normal metabolism have, as a rule, passed through a larger number of cell generations than tissues which are still active functionally.

The question, therefore, is, What are the external or internal influences (apart from the length of life of the individual as a whole) which tend to induce abnormally rapid cell division in, and consequently ageing of, epithelial tissues? Among such influences we must include mechanical and chemical irritation, X rays, alcohol, soot, arsenic, betel nut, tobacco, clay pipes: all these are chronic irritants. And in so far as chronic irritation acts as a predisposing

[2] Transactions of the Leicester Medical Society, 1886.

cause of epithelial cancer, it does so by disturbing the nutrition of the epithelial cell and by causing rapid cell division, and in this way by bringing about cell senility.

The same senile influence is exerted on epithelial tissue by the frequently repeated exercise under special abnormal conditions of otherwise normal physiological functions. Thus cancer is more frequent in the uterus and mammæ of women who have borne and suckled children than in women whose organs have not passed through such cycles of increased and diminished cell growth, cell division, and cell destruction. These last three processes are the three conditions which favour the occurrence of variation and selection among organisms exposed to them, and of the abnormal conditions associated with their exercise, stasis of secretion and sudden arrest of function seem to be the most important.

Joining these facts together we find that cancer characters tend to appear in epithelial tissues which are nearing, or which have reached, the hereditarily fixed limits of functional capacity—that is to say, among cells which exhibit diminished capacity for cytoplasmic function and increased capacity for nuclear division of an abnormal kind. We use the word *among*, and not in, advisedly, because there is no reason to suppose that the worn-out, senile, epithelial cells themselves become cancer cells. We must rather suppose that these worn-out cells, which are ill adapted to the changes in the environment associated with the origin of cancer, perish, and are removed, and that their place is taken by younger undifferentiated cells, and that among these younger cells some possess capacities of vegetative growth which are of great value in enabling them to survive under the altered conditions, and during the struggle for room and nourishment going on with neighbouring cells. Of these abnormal characters, diminished capacity for cytoplasmic function and increased capacity for nuclear division seem to go hand in hand. As cytoplasmic function decreases assimilation increases, and as the nucleus ceases to direct cytoplasmic activity along functional lines, it tends to be exercised in initiating rapid and disorderly cell division.

Having thus indicated some of the main features which distinguish the cancer cell from the normal epithelial cell, having associated the different bodily conditions and the external influences found during the origin of cancer with one common factor, disturbance of nutrition, we are now in a position to ask whether the conditions, under which these new cancer characters appear in cells, suggest a "variational and selectional" or a "use acquirement" origin in the case of epithelial cancer.

We wish to ascertain, in other words, whether the older epithelial cells which have been exposed to the disturbed nutrition, to the mechanical or chemical irritation, to the abnormal activities of other cells, or to abnormal influences, reaching them from the body as a whole, or to the influences, whatever they may be, which predispose to cancer, we wish to ascertain whether these cells themselves become cancer cells, or whether during the struggle for existence, room, and nourishment, the increased cell proliferation, and the destruction of cells of less vegetative capacity, variations occur among the younger generations of epithelial cells exposed to the environmental change, some of which, being more adapted to live and multiply under the new conditions, survive as cancer cells.

If we analyse the changes which occur in epithelial tissues during the so-called pre-cancerous stage, we find new characters in some only and not in all the epithelial cells exposed to the changed conditions. Cancer seems, in some cases at least, to originate in a very small cell group, or even in a single cell, as we should expect if it originates in variation and not in use acquirement. In the second place, cancer is associated with the death and removal of large numbers of epithelial cells Destruction of epithelial cells is constantly associated with all kinds of chronic irritation of epithelial tissues—in X ray dermatitis, in ulceration of epithelial surfaces due to microbic infection, in leucoplakia of the labial, buccal, and lingual mucous membrane, induced by alcohol, tobacco, syphilis, and the clay pipe, in the erosion of the os uteri the result of septic uterine discharges, in the involutionary changes which accompany chronic inflammation of glandular organs, such, for instance, as chronic mastitis. All these changes, which make up what we know as the pre-cancerous stage, are associated with the atrophy, death, and removal of large numbers of epithelial ce

These facts strongly suggest that the cancer character originates in the younger actively proliferating cell layer rather than in the older more highly differentiated layer of epithelial cells which constantly perish and are removed. They suggest also that the cancer character arises among these younger epithelial cells as a variation rather than as an acquirement. In this sense the cancer response is the "indirect" rather than the "direct" result of some environmental change.

Such, then, in brief outline, is our conception of the cancer process as it originates in epithelial tissues.

Cancer of the Connective-tissue Type.

We now come to the consideration of the connective-tissue or mesoblastic cell, and the blastomata which arise in connexion with it. In the first place, the mesoblastic cell only responds to two environmental factors, the nutrient medium, the blood- or lymph-stream on the one hand, and the activities of other cells, epithelial or mesoblastic, on the other.

I. *External World Factor.*

Unlike epithelial cells, the connective-tissue cell has no relationship with the outside world; consequently, it does not, as a rule, show any differentiation of cytoplasmic substance into free and attached, or assimilating and secreting surfaces. The whole cell surface is bathed by the nutrient medium. It does not elaborate any external secretion because it has no free surface from which it can discharge mucus or enzymes on to the exterior of the body.

Even when it elaborates and deposits formed and inert material, such deposition occurs for the most part symmetrically, unless the irregular incidence of the stimuli interferes and brings about a corresponding inequality of deposition. This occurs in response to the unequal environmental influences of contact, pressure, and strain, as well as chemical stimuli. Even in such circumstances, the unequal stimulus which causes the unequal response is the outcome of the activities of an internal, cellular, and not an external outside world environment.

It is true that the endothelial and mesothelial cells line tubes and cavities which contain blood and lymph, but these nutritional streams exert upon the cells the influences of a nutritional and not an outside world influence, subject, of course, to alterations in the blood and lymph due to the addition of nutritive or chemical substances which reach it from the outside world.

II. *Neighbouring Cell Factor.*

When we come to the next environmental factor, the stimuli supplied by the activities of neighbouring and other cells, we find that the mesoblastic cell is peculiarly sensitive to such influences, especially to the activities of cells of the epithelial type.

Observations made during the experimental inoculation of cancer in mice show that such inoculation in any susceptible animal is followed by three definite phases: an early phase during which successful inoculation may still be practised on the same animal, an intermediate phase during which such inoculations regularly fail, and a terminal phase in which re-inoculation is again successful, and in which auto-inoculation and metastatic deposits occur. These alternating phases of susceptibility and resistance to the growth of the epithelial cancer cell on the part of mesoblastic cells afford clear evidence of an attempt on the part of the connective tissues to form a defensive reactionary growth which is ultimately overcome by the increasing growth and activity of the cancer cells. They suggest the evolution of a capacity of adaptive response on the part of cells of both groups, the invading cancer cells on the one hand, and the invaded mesoblastic cells on the other, of the same kind but of a more specific nature and with less successful result, as that made by the phagocytes to the microbes of disease.

The fact that secondary growths are less completely limited by fibrous investment than primary growths suggests either increased malignancy on the part of cancer cells which compose these metastases or of enfeebled resistance on the part of the connective tissues which surround them. In connexion with the occurrence of metastasis it is interesting to note that the quality of the resistance made by the mesoblast cells depends on specific, racial, and hereditarily transmitted characters. It is increased by age, and it can be diminished and eventually overcome by the continued

presence and growth in the tissues of a primary cancerous tumour.

Moreover, it is possible, as Bashford has shown, to raise the stroma-compelling capacity (i.e., the virulence) of epithelial cancer cells towards the resistance-offering capacity of the connecting tissues in any race of mice by passing the grafts through a series of inoculation generations in a number of individuals of the same race. This shows that it is possible to raise the malignancy of epithelial cancer cells by cultural methods, in the same way that the virulence of any disease organism can be raised, the difference being that in the case of cancer the change effected is a specific and not a general one, as in the case of disease organisms. This fact, again, supports the variational and selectional origin of cancer cells.

The labours of Ehrlich and Bashford have further shown that under certain circumstances of repeated inoculation the mesoblastic cells respond to the foreign epithelial cancer cell by the growth of a cellular tissue of low grade development indistinguishable histologically from sarcoma—that is, from cancer of the connective tissue type. This occurrence (if the interpretation placed upon it by the above observers is a correct one) supplies evidence of the origin of cancer in mesoblastic cells as the direct result of an alteration in the activities of certain epithelial cancer cells which for the time being form the cellular environment of the mesoblastic cells. There is no record of the occurrence, at any rate in the human subject, of the reverse condition. That is to say, no one has seen the occurrence of cancer characters in the epithelial cells of any organ as the result of the growth of secondary sarcomatous deposits in such an organ.

Finally, we must remember the specific nature of the cancer response. The fact that cancer cannot be transferred by inoculation from an animal of one species to an animal of a different species, and that inoculation is frequently unsuccessful when practised on an animal of a different variety, affords strong evidence of the delicacy of the balance of tissue relationship between epithelial and connective tissue cells. For the viability of the cancer graft the little aggregate of abnormal epithelial cells depends on the attitude taken up by the mesoblastic cells of the host in regard to the graft. If these react moderately and in a specific manner and form a nutrient stroma the graft lives and grows; if they react aggressively and form a fibrous tissue the graft dies.

All these facts illustrate the peculiar sensitiveness of the mesoblastic cells to the cellular element in their environment, and the alterations which take place in this sensibility are of an adaptive kind. But the conditions of the "sarcoma response" differ from those of the "cancer response" in yet another way in regard to the cellular element in the environment.

Age Incidence.

The age incidence of the disease is different in the two cases. While epithelial cancer tends to originate in epithelial tissues that are becoming senile, it tends to thrive best in connective tissues that are young. On the contrary, connective-tissue cancer tends to originate in the connective tissues of young individuals. Sarcoma has long been regarded as a disease of infancy, childhood, and young adult age. Roger Williams has collected many observations which confirm the accuracy of this clinical inference and which also, on careful inquiry, suggest further important differences between epithelial and connective-tissue cancer from our present adaptational point of view.

If we take benign tumours of the connective-tissue-cell type we find that chondromata are frequently multiple, often bilateral, and sometimes symmetrical. The fibromata are frequently multiple, often bilateral, and, in the case of the multiple fibromata of nerves, are probably congenital in origin. Moreover, these tumours have been noticed in a considerable proportion of cases to take on a sarcomatous type of growth. Osseous tumours are notably bilateral and often symmetrical, and what is most important hereditary transmission can be demonstrated in some cases. Thus, Reclus reports the case of a man with epiphysial exostoses, whose sister and three sons also showed the same peculiarity, the sister's daughter was also affected, also her four children, and seven of the grand-children.

Non-malignant ovarian tumours of the dermoid and papillary and cystic forms are all frequently bilateral. When we consider malignant tumours of the connective-tissue-cell type we find evidence that sarcomata tend to be bilateral in a greater proportion of cases than epithelial cancer in the same organ. Thus Gross reports 1664 cases of mammary cancer in which only two were bilateral, while in 156 cases of mammary sarcoma three were bilateral. In the ovary malignant tumours are frequently bilateral, but even here ovarian sarcomata, especially the round-celled variety, tend to be bilateral in a greater degree than other malignant growths. They occur chiefly in early life. In the testes round-celled sarcoma again is the usual and more frequent form of bilateral tumour. On the other hand, teratoid and dermoid non-malignant testicular formations do not seem to be bilateral.

Of the early life renal tumours, bilateral sarcomata are the most frequent. Glioma of the retina is frequently congenital and usually double-sided, and curiously and most important as in the case of epiphysial exostoses it is often hereditary. Newton records a family of 16 persons, of whom 10 died from glioma of the retina. The pigmented choroidal sarcomata are occasionally bilateral. Myeloid sarcoma of the lower jaw is sometimes bilateral.

Putting these facts together we find that tumours of connective-tissue type are often bilateral, and sometimes symmetrical in arrangement; they are sometimes congenital and usually occur in childhood or early adult life, and they are occasionally familial or hereditary. Now bilaterality and congenital origin suggest developmental and general, rather than environmental and local influences as factors in causation; while hereditary transmission, especially in the ocular glioma cases, also points in the same direction. Just as, on the other hand, the absence of bilateral arrangement and early life origin in the case of epithelial cancer suggest a diminished influence on the part of such factors, though developmental tendencies may presumably operate even here as predisposing causes, in so far as they exert an influence on the epithelial tissues to yield to or to resist the senile change.

In the same way mechanical and chemical irritation by external agencies, which play so important a part in the causation of epithelial cancer, must be of secondary importance in the case of cancer among cells which have no external world factor in their environment. But if, on the other hand, we recall the peculiar sensitiveness of the mesoblastic cell to the life activities, physical and chemical, of the neighbouring cells we are on firmer ground. This sensitiveness to "other cell" activity seems peculiar to mesoblastic cells of certain connective-tissue types, just as sensitiveness to the secretions of micro-organisms is peculiar to the phagocyte, another specialised type of mesoblast cell. It is, indeed, possible that the supposed association between traumatism and sarcoma may really depend on a reaction on the part of the connective-tissue cells to the abnormal activities of the extravasated red and white blood cells at the site of the injury rather than on the injury done to the connective-tissue cells themselves.

Nutrient Medium.

We must not omit to consider the powerful influence exerted by the nutrient medium, the remaining factor in the mesoblastic cell environment.

Looked at biologically, this nutritional factor resolves itself into a cytological one. It becomes a question of changes in the cellular elements in the blood and lymph streams, and of changes in the secretions or excretions poured by the body cells of various types into these two streams of nutrient material. The difference in chemiotactic capacity between cancer and sarcoma cells is of much interest from this point of view, and cannot, I think, be wholly explained by a difference of primary location in the two kinds of cancer cells in regard to the lymphatic and blood channels. The epithelial cancer cell perishes in the blood stream and flourishes in the lymph stream, while the connective-tissue cancer cell flourishes in the blood stream more luxuriously than it does in the lymph stream, and this difference in relationship would seem to depend partly on a difference in sensitiveness to the activities of the endothelial cells which line the lymphatics and the capillaries respectively.

Finally, the fact that increased vegetative growth and decreased functional activity, the two fundamental characteristics of malignancy, are present in both types of cancer,

not only confirms the suggestion that the cancer process is an adaptive response in both cases, but it also suggests that the particular environmental phase to which the cells are reacting, and to which, so to speak, they are trying to become adapted, has this feature in common in the two types—namely, that it is an environment which favours vegetative activity and does not favour functional activity. While the further facts—namely, the slender association of mesoblastic cells with an external environmental factor, the slight influence of external stimuli in the causation of connective-tissue cancer, the occurrence of bilaterality, and congenital origin, and occasional hereditary influence in sarcomatous tumours—all these suggest the importance of developmental factors and nutritional influence as opposed to external stimuli in this disease.

Moreover, the absence of any keen struggle for cellular existence and of active cellular proliferation, or of extensive cellular destruction, during the pre-cancerous stages of connective-tissue cancer suggests that the conditions under which sarcoma originates are not identical with those under which cancer of epithelial type originates. And in view of the special sensitiveness of mesoblastic cells to the activities of other cells it is possible that it is in this direction that the explanation of the differences in the origin of cancer in the two cases is to be sought.

Benign Tumours.

We must now consider the blastomata which arise among cells of epithelial and mesoblastic type, and which are not characterised by malignant features.

Looked at from the standpoint of adaptational response the difference between benign and malignant tumour formation becomes a question of degree. It depends on a difference in capacity on the part of the cells which compose the tumour to live and multiply in an abnormal environment of a special kind. For instance, the cells of the epithelial adenoma of malignant type are able to live and multiply in an environment formed by cells of quite another type, exercising activities of another kind, such, for instance, as that provided by the mesoblastic cells of the lymph gland. The cells of the epithelial adenoma of the benign type, on the other hand, have not got this capacity, they can only live and multiply, and that to a limited extent, among cells and tissues of the type to which they themselves belong.

It is true that the cell character and potentiality have been so far modified as to enable these cells to grow in a more or less orderly fashion in an environment in which the external world influence has been reduced to a minimum, and that as a consequence such cells have lost much of their capacity for normal function and normal secretion. But in spite of this partial change they are quite incapable under the ordinary conditions of benignity of living and dividing in the environment provided by a lymph gland, a situation in which cancer cells can flourish.

In the same way the cells of the benign tumour of the connective-tissue type, the chondroma, the osteoma, and the fibroma, resemble the cells of the benign epithelial tumour. Under normal conditions of benign growth and homotropism they can only flourish when growing in a community formed by cells of their own type of tissue.

It is true also in the case of these benign blastomata of hylic type that the new characters acquired by the cells which compose them enable them to grow and divide in a more or less orderly fashion in an environment which is not normal, and in which the relationship which normally exists between mesoblastic tissues of different sub-types has been modified by locally acting causes such as traumatism, or more general factors such as developmental potentialities and possibly abnormal internal secretions. But they do not while remaining benignant vary beyond this point. The cells composing a fibroma or osteoma of benign type cannot live and multiply in the environment provided by the lymph gland tissue, while the cells of the malignant fibroma or osteoma can live and grow in such unusual surroundings.

Teratomata.

So also with the teratomata. The cells which give rise to a teratoma are cells possessed of certain characters analogous to those of germ cells, from which probably in some aberrant form they are directly derived. They are cells which have inherited or acquired a capacity to live and multiply and exhibit teratoid characters in surroundings and under conditions unusual in germ cell development.

We are ignorant of the causes which start such aberrant or displaced cells on a course of abnormal cell division and tumour formation, but we are probably right in regarding the whole process as a response (restricted within the limits of hereditary potentiality) on the part of such cells to the abnormal environment in which they are placed. Moreover, these teratomata, which are really blastomata arising among toti-potential cells, exhibit the same transitional characters and the same tendency to diverge into malignant and benign types as the blastomata which arise in multi- or uni-potential cells—that is, in cells of epithelial or connective-tissue type.

Chorion-epithelioma is especially interesting from this point of view. Here is a blastoma arising among uni-potential cells, of extraneous and fœtal, or rather trophoblastic, origin, which have acquired a capacity to live and multiply in situations and under conditions foreign to their normal habitat. They are no longer sensitive to the restrictions to growth of a homotropic kind imposed on such cells by the internal secretions, associated with the metabolism of the lutein ovarian tissue, or the fœtal tissues, while they have at the same time acquired increased vegetative capacity. In the one form of activity they form the benign hydatid mole, in another more active form they give rise to the extremely malignant chorion-epithelioma, and the point of interest is that between these two extremes they exhibit transitional characters, intermediate varieties, half-way steps, as it were, on the way to the more completely adapted form shown by the malignant type.

Thus, while the structural and functional differences which separate the extreme types of benign and malignant blastomata represent different degrees of adaptive capacity, on the part of the cells which compose them, to environmental change of a slight or profound character, there are tumours of an intermediate class in which the cells show transitional characters, and in which it is difficult to decide whether they should be included in the benign or the malignant group.

Surgeons are familiar with tumours which originate as benign growths, and which for many years continue to exhibit such features, but which, under the influence of certain imperfectly understood environmental stimuli, of which imperfect removal seems to be one of the most important, begin to vary away from the benign type and to exhibit a capacity for vegetative and peripheral as opposed to central growth, and which under certain conditions may vary further still, and, losing their homotropic tendencies, may originate metastatic growths. Many observers have noted that among benign tumours the chondromata are especially liable to give rise to such secondary growths; this peculiar tendency may well be associated with the peripheral mode of growth characteristic of such tumours. Kirche and others have described multiple metastases in primary fibromyoma of the uterus of originally benign type.

Benign tumours of epithelial type also give rise to secondary deposits under special conditions thus: Adami, Finley, and Russell have shown that the secondary growths derived from benign adenomata of the liver sometimes display malignant characters. There is, indeed, every reason to suppose that cells can and do escape from benign tumours just as they do from placental chorionic tissue in normal pregnancy, or just as they do constantly in the case of malignant growths, and the question of their subsequent growth and proliferation in the new situations would seem to depend on a difference in capacity between benign and malignant cells to overcome the resistance offered by the invaded tissues.

But not only do the cells of benign tumours under certain conditions exhibit this capacity to originate detached growth foci, the apparently normal cells of an organ like the liver or the thyroid may, under certain circumstances, exhibit the same tendency. The attempts at cell regeneration which accompany the process of biliary cirrhosis seem to provide the conditions favourable for the origin and growth of new liver cells capable of functioning as normal liver cells or under other conditions of forming benign adenomata, or, again, of adeno-carcinomatous tumours capable of originating metastases in other tissues.

This development of liver cells of transitional types during cirrhosis, a process characterised by cell destruction, cell proliferation, and nutritional impairment, is of especial interest in connexion with our present conception of cancer as an adaptive response, depending on variation and selection

among cells exposed to environmental change. It also serves as a connecting link between blastomatosis on the one hand and cell metaplasia and blastomatoid hypertrophy, and with regeneration of tissues and organs, and the process of repair which accompanies the healing of wounds on the other.

All such processes thus fall into line as examples of adaptive response on the part of cells of different types to different conditions. The same is true of thyroid tumours. Adenomatous growths, structurally benign, of thyroid origin have been found in the cancellous tissue of bones in various situations, displaying all the destructive and vegetative activities characteristic of malignant tumours. On the contrary, thyroid growths, undoubtedly malignant, frequently elaborate colloidal material in newly formed acini, the cells of which, though of malignant type, have retained some of the functional capacity of normal thyroid cells. Moreover, in other situations typically malignant primary tumours of considerable age and size have been encountered unaccompanied with any evidence of secondary deposit. Moreover, the malignant tumours themselves afford examples of every degree of malignity, from the slowly growing atrophic to the rapidly growing, widely disseminating virulent type.

The peculiar tendency of thyroid cells to grow in bone is another example of the delicate, and in some cases specific, nature of that relationship between tissue cells of different types of which we have already spoken, and we can only suppose that cells are under certain circumstances carried from thyroid and liver benign tumours, as they are under other circumstances carried from other organs and other tissues, such as chorionic villi, and come to rest in many situations, but only those cells survive and multiply which find themselves in tissues and in situations which provide an environment favourable for their growth.

Thus we are led to regard benign and malignant tumour formation as a process of adaptation on the part of certain cells to environmental factors which concern their welfare as cells rather than the welfare of the organism as a whole.

Cancer Character.

The change of character which distinguishes the cancer cell from the normal cell is of a retrogressive rather than a progressive kind, or rather largely retrogressive and partly progressive. It is a change comparable with that by which a parasite becomes adapted to an environment which affords diminished scope for functional activity, and increased facility for the assimilation of nourishment.

In the epithelial cancer cell, increased vegetative activity is obtained at the expense of diminished power of secretion and reaction to external stimuli. In the connective-tissue cancer cell vegetative activity is obtained at the expense of structural differentiation of the cytoplasmic substance. Thus in cancer there is a disturbance of the normal relationship between nuclear capacity for directing cytoplasmic metabolism along functional lines, and nuclear capacity for initiating cell division.

In proportion as the cytoplasm ceases to be sensitive to use stimuli and becomes increasingly sensitive to nutritional stimuli, in such proportion the nucleus ceases to direct cytoplasmic activity along functional lines useful to the organism, and directs it along lines of assimilation useful to the cell. In proportion as the cytoplasm ceases to respond to the activities of neighbouring cells, nuclear division escapes from the restrictions to too frequent cell division normally imposed on healthy cells by the activity of neighbouring cells of different type. Moreover,[3] all these increased capacities in one direction and diminished capacities in other directions which go to make up the cancer habit are qualities possessed in somewhat less degree by normal cells. Some facts noted by Ehrlich seem also to suggest that under certain circumstances the cells of a repeatedly inoculated mouse cancer may partly revert to the condition of normal cells.

All these facts strongly support the conclusion that the complex cell change that we associate with cancer has been built up by variational changes from the normal type, and that one of the stages passed through is represented by the various forms of benign growth. They suggest that the external cause of epithelial cancer is to be sought in some change in one of the three factors which make up the environment of the epithelial cell, in interaction with an internal factor, the potentiality, hereditary or acquired, of the cell exposed to the change. Whereas in cancer of the connective-tissue type, cell potentiality as affected by developmental and hereditary influences seems of more importance than environmental change.

The cancer response differs from the response made by germ cells to environmental influences in this respect. The germ cell and the cancer cell have both ceased to respond to "use," and only respond to "nutritional" stimuli; but in the cancer cell, unlike the germ cell, the change is brought about by retrogressive variation to a parasitic habit, with the loss of a capacity to undergo normal development which is retained by the germ cell.

Summary.

Thus we are led to describe blastomatosis as an adaptive response on the part of individual cells, or cell groups, to environmental change of three kinds: alteration in the stimuli which reach the cell from the outside world; alteration in nutrition; alteration in the activities of the other cells which compose the organism. This adaptive response may be "indirect," the result of variation among the cells exposed to the changed conditions accompanied by selection of an *inter*-cellular kind, or it may be "direct," and the result of a process of variation in the physiologically differentiated parts which compose the individual cell, accompanied by selection of an *intra*-cellular kind, in which case it represents a "use acquirement."

The new cell characters which so arise may be grouped in two main divisions—one characterised by typical growth including all the histological varieties of benign neoplasms from teratoma to neuroma, the other characterised by atypical growth including the malignant types. But between these two groups there are numerous tumours composed of cells presenting transitional characters. Yet, again, the second group, characterised by atypical growth, may be divided into neoplasms composed of cells of epithelial type, and neoplasms composed of cells of connective-tissue type. And between these two groups there are again connecting links, for the malignant tumours which arise from cells of primary mesoblastic and secondary epithelial origin tend to exhibit transitional characters.

Of the two factors concerned in the origin of malignant growth (cell potentiality and environmental influence) environmental influence plays a large part in the genesis of cancer, cell potentiality in the genesis of sarcoma. Of the environmental factors concerned, outside stimuli exert a much larger influence in the genesis of epithelial than of connective-tissue cancer.

Other Theories of Cancer.

In conclusion, we must now compare the account of blastomatosis here propounded with previous descriptions of tumour formation put forward by other observers.

Cohnheim and Ribbert.—"Pre-" and "post-" natal cell displacement, either alone or in association with diminished growth resistance, have been put forward by Cohnheim and Ribbert as causes of tumour formation.

Parasitic.—For some time the theory of parasitic infection held the field.

Von Hansemann.—This author suggested "anaplasia," the formation of new races of cells possessed of abnormal characters, in association with an abnormal distribution of nuclear cell material, as a cause of cancer.

Adami.—Stress has been laid by Adami and others on "habit of cell growth" and on the process of cell undifferentiation as it is present in metaplasia and normal cell division.

Oertel.—Assuming two kinds of nuclear material, one controlling function, the other vegetative activity, Oertel associates the loss of functional activity characteristic of cancer cells with the loss of the former kind of nuclear material during the irregular cell mitoses which accompany malignant growth.

Marchand.—Attention has been drawn by Marchand to the marked difference in potentiality between the normal embryonic cell and the embryonic cell of neoplasmic growth, which must be taken into account in any attempt to explain blastomatosis as a return on the part of certain body cells to embryonic characters.

Hauser.—From a minute examination of the changes shown by the epithelial cells of intestinal new growths Hauser put forward in 1890 the suggestion that the cells of new growths are the descendants of some single cell which, during the course of ontogenetic development, has "mutated"

[3] Gould, Bradshaw Lecture, THE LANCET, Dec. 10th, 1910, p. 1665.

or varied away from the normal character, and has given rise to cell descendants in which these new characters persist, and among which vegetative activity is one of the most important. He also associated this mutational change with excess of cell nutrition.

Adami.—Dissatisfied with any attempt to explain the origin of the new characters found in neoplastic cells by chance variation or mutation, Adami would regard such mutational change as a direct response on the part of such cells to environmental influences. Believing, further, that no one environmental stimulus is responsible for the whole cell change, Adami considers that a number of different influences may combine to cause the cancer change. Among these he enumerates the influence of cell displacement, chronic inflammation, irritation, mechanical or microbic in origin, cell senescence, impaired cell nutrition leading to cell proliferation, in association with preceding changes in the underlying connective tissues in the case of some epithelial cancers, while among subsidiary influences he mentions diminished external growth resistance and altered cell secretion.

H. Ross.—More recently H. Ross, impressed by the powerful influence exercised by the products of cell death in association with certain chemical substances of an alkaloidal nature, in initiating cell division in leucocytes and lymphocytes and some other cells, has suggested that the rapidly recurring division of cancer cells may be associated with a like cause.

Such are some of the many and various theories which have been put forward at different times to explain the origin of tumour formation, and incidentally the origin of cancer.

The present contribution makes no attempt to put forward any new explanation of the cause of cancer. It must rather be regarded as an attempt to consider the cancer problem from a wider biological standpoint by directing attention to the adaptational nature of the new characters acquired by cancer cells, and as an attempt to analyse some of the conditions under which benign and malignant tumour formation takes place.

The result of such an analysis goes to show that cancer, like all "new growth," must be regarded in the light of a response of an adaptive kind on the part of certain cells or cell-groups of varying potentiality, to changes in their environment. It suggests that in epithelial cancer, at any rate, this response takes place under the same conditions as those which are associated with the occurence of variation and selection among other organisms when exposed to environmental change and where evolution of new characters is taking place, especially in response to changes in the external environment. And the suggestion is therefore made that blastomatosis, including cancer and certain other forms of cell multiplication, takes place under the influence of the same evolutionary factors—namely, variation and selection of the "inter-" or "intra-" cellular kind.

The old inquiry still remains. It is the ascertainment of the kind of environmental influence on the one hand, and the special factor, hereditary or acquired, in cell potentiality on the other, which are independently or conjointly responsible for initiating the process whereby the new characters arise "innately" in, or are "acquired" by, cells engaged in neoplasmic growth.

Leicester.

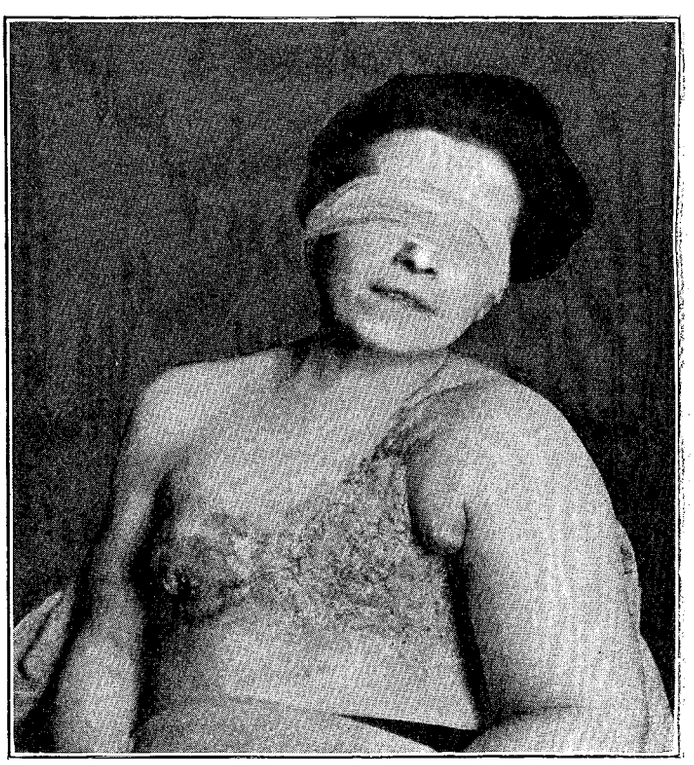
DIFFUSED CANCER OF THE FEMALE MAMMARY AND THORACIC INTEGUMENT ("CANCER EN CUIRASSE").

BY SIR GEORGE THOS. BEATSON, K.C.B., M.D. EDIN.,
SURGEON TO THE GLASGOW WESTERN INFIRMARY AND TO THE GLASGOW CANCER HOSPITAL.

THE clinical experience of most surgeons is that primary carcinoma of the mammary integument is not of frequent occurrence, and that the most usual site of it when it does occur is the region of the nipple and its areola. Its occurrence in this latter situation is what might be expected, seeing the rôle irritation plays in the development of malignant disease, for the nipple and the skin around it is often the seat of cracks and fissures that are not always easy to heal and that are sometimes submitted to somewhat drastic measures of treatment. Should primary cancer of the nipple show itself it may be in the form of a squamous-celled epithelioma, or of a glandular carcinoma, originating in the epithelium (1) of the sebaceous glands or (2) of the galactophorous ducts. It is in connexion with cancerous changes in the duct epithelium that Paget's disease is a recognised factor. Commencing as an eczematous condition of the nipple and areola of a purely inflammatory nature, it in time brings about in the epithelium of the ducts alterations which spread to the deeper parts of the breast, with the result that we have the acini becoming distended with proliferating epithelium and true carcinoma mammæ is developed.

There is, however, another form of cancer of the mammary integument which is seen from time to time and is characterised by a dense unyielding leather-like state of the skin of the thorax. Although referred to by Howard of the Middlesex Hospital in 1792, attention to this class of case was specially drawn by Velpeau in 1838, who described it under the name of "ligneous cancer" in plates, or *diffused* over the mammary integument, and he termed it "cancer en cuirasse." He stated that he had often met with it, and he emphasised as its characteristic the brawny (*ligneuse*) change present in the skin. He regarded the cases as illustrative of the wide area that a carcinoma may involve by continuous spread from a central focus. Some cases have been published that have been regarded as primary examples of this condition, but they are very few in number and are by no means conclusive. As a rule, the affection is secondary, and either accompanies carcinoma of the mamma or makes its appearance after the removal of a breast for malignant disease. At the Glasgow Cancer Hospital I have met with four such cases, the first one, shown in Fig. 1, being admitted on March 25th, 1895. It was of a secondary nature and was of three months' duration, having shown itself nine months after the removal of the left breast for a cancerous growth. The illustration (Fig. 1)

FIG. 1.



Typical "cancer en cuirasse."

shows the extensive involvement of the mammary integument on the left side and its extension to the right breast, which was tense and tender and was entirely occupied by a firm round swelling, reddish all over the surface, with some œdema in the surrounding tissues. Part of the cancerous area on the left side of the thorax had ulcerated, and there was present that marked œdema of the upper extremity which is such a constant and important feature of this affection. There was also present some fluid in the left pleura. The progress of the case was rapid. The notes say that the