applied in colleges and halls to young women at from 18 to 24 years of age. Admirable culture is supplied in these colleges and halls, but they, too, have their risks notwithstanding that their pupils are all picked lives. The suicide of a pupil who had just undergone examination at one of them was reported two months ago. I must, however, even now express my belief that the University of St. Andrews, in deciding, as it has lately done, to open all its classes in arts, science, and theology to women as well as men, has taken, not a retrograde step—for our ancestors never did anything so foolish—but a downhill step towards confusion and disaster. Its now empty benches may be thronged with pupils, its professors may batten for a time on duplex fees, but the attempt to educate young men and women, not only on the same lines, but in the same coaches, cannot but prove injurious to both. "What was decided amongst the prehistoric protozoa cannot," it has been well said, "be annulled by Act of Parliament," and the essential difference between male and female cannot be obliterated at a sweep of the pen by any *Senatus Academicus*.

THE MORTON LECTURE ON CANCER AND CANCEROUS DISEASES.

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THE ETIOLOGY OF CANCER.

MR. PRESIDENT AND GENTLEMEN,—I understand that the Morton lectureship was established with the view, in the first instance, that the lecturer for the time should gather together and give in the form of a summary any fresh light that has during the preceding year been shed on the subject of cancer. Beyond this, however, the object of the founder appears to be to stimulate thought and research in connection with a disease, the importance of an accurate knowledge of which is at present only equalled by the futility of all the efforts that have been made to elucidate even a few of the problems that a most cursory glance at the subject must at once suggest.

We owe to histology and to statistics almost all the knowledge concerning cancer that has hitherto been acquired, and most of the answers to such questions as have been solved. The clinician, to whom cancer has been a study of most absorbing interest, has done all that was within his power, but beyond determining the bounds of the periods of life during which it may occur, and the nature of the hereditary predisposition of certain subjects and tissues, this all has been but little. Even the attempts to associate the growth of cancer (and, by cancer, I shall to-day mean cancer in the strictest limitation of the term) with any specific causal agent has hitherto failed, and I must confess that, until quite recently, I have remained strongly of the opinion that, although cancer may possibly be the result of certain forms of irritation, it can scarcely be looked upon as due to the vital activity of any specific micro-organism, whether animal or vegetable; in fact, I am not yet prepared to depart entirely from this position, though I must acknowledge that comparatively recent observations have been made which, if ultimately confirmed, would go far to limit the range of irritants which possibly may give rise to the proliferation of the special tissues with their special arrangement so characteristic of cancerous growths.

It will be well that we should for a moment turn our attention to some of the work that has already been done in this domain. A former distinguished Morton lecturer, the late Mr. John Marshall, pointed out that up to his time most of the advances made in our knowledge of cancer were the outcome of a close study of its histological structure, and that no advance could possibly have been made as regards the classification of malignant tumours until we had obtained an accurate knowledge of their essential morphology. Virchow's doctrine that all tumour and other cells

have their homologues in the embryonic or adult tissues of the normal body renders it necessary that we should determine how far the form and arrangement of the tissue-elements correspond with any of these, and in what respect they agree with such structures during the process of development of the organism, and at what periods and under what conditions such homologues occur. Departing somewhat from this doctrine, Mr. Marshall described the tissues met with in cancer as not resembling those in process of development, but corresponding rather to tissues in a state of anarchy. Whether we accept one idea or the other—and I must say I incline to Virchow's original idea—the conditions met with in cancer can only be initiated when two different sets of factors are brought into play: (1) There must be altered conditions within the tissues, impaired nutrition, impaired vitality, deficient controlling power either from within or without; and (2), almost equally important, there must be some special or long-continued stimulus, the exciting cause of proliferation from without, which leads to the formation of tissues of an embryonic or an anarchic type; and whether we speak of growth or of anarchy, these two sets of embryonic factors will always have to be reckoned with.

What I have to say to-day may be arranged under three heads:—

1. The conditions within the tissues that may predispose to the formation of cancerous tumours.

2. What we know as to the nature of the irritants that are now assumed to play a specific etiological part in the production of cancers.

3. What is to be gathered in respect to the treatment of cancer from recent researches on the subject.

It has frequently been insisted upon that the nucleus plays a most important part in determining the multiplication of cells. We may say, indeed, that the nucleus is the active part of the cell, in the sense that it is always the first part of the cell to undergo division. From the extraordinary size and distinctness of the nucleus and nucleolus of the cancer cell, some have gone so far as to indicate that these are practically sperm and germ cells respectively. Within these there is undoubtedly during the normal life of the individual a power of multiplication, a power which, however, varies greatly at different stages of this life. When this power dies out, under normal conditions, a man is said to die of old age, and it is necessary for the continuance of the species that there should be a recurrence to a process of direct reproduction through the well-nourished ovum and the highly differentiated sperm cell, by the conjunction of which the cycle is recommenced. Here we have, just as really as in the case of certain parasitic organisms, a kind of cycle or alternation of generation. Although asexual reproduction can go on for a time, there comes a point at which it is necessary that sexual generation should step in. This takes place even under normal conditions, but it must be remembered that under certain conditions and at certain periods of life the nutrition and reproductive powers of different sets of cells may be profoundly modified in one direction or another. At one time, as has often been insisted, the connective tissue cells are most active, at another the epithelial cells. It must be further recognised that we may come into the world middle-aged men and women as far as our tissues are concerned. The ovum or the sperm cell, or both, have had their nutrition and activity so diminished before they came together, that the resulting individual has not had a fair start in life, whilst even those who have begun with everything in their favour as regards embryogenetic conditions, have so suffered from impaired nutrition and from disease that their tissues in turn are old before their time; we have premature senescence, and a marked liability to those diseases associated with old age. Only in this way can we account for many of the anomalous conditions that make their appearance in the practice of the surgeon, and are tabulated in the statistics of all those who have paid attention to the subject.

More than forty years ago, when Virchow brought forward his epoch-making doctrine that in all pathological, as in all physiological processes, cells beget their like, he at the same time shadowed forth the idea, that, although all cells are begotten of other cells, the progeny only resemble their parents:

when they are produced under general conditions and surroundings, circumscribed within certain very definite limits. We now accept it as a well-authenticated fact that by varying the conditions of nutrition, the facilities for excretion, and the nature and amount of stimulation or irritation, we can, to a certain extent, control or alter the character of the cells produced by a given set of tissues. Of this we have an admirable example—first pointed out by Goodsir and Redfern—in cartilage and tendon; here the behaviour of the cells and their progeny in the healthy condition is perfectly different from their behaviour when they are subjected to irritation; whilst it is an equally well-known fact that, if the irritation be removed, the cells that are afterwards formed gradually assume the characters of normal cartilage cells.

I believed at one time that this law of heredity did not work in one direction only, and I still think it possible, though, perhaps, scarcely proved, that if cells are formed generation after generation under the action of an irritant, their specialisation might be gradually interfered with, a less and less irritant being sufficient to keep up the new form of cell, until eventually the acquired form may become more or less permanent. This might serve well enough as a working hypothesis were we still unaware of the fact that in almost every other department of pathology some specific irritant, which is capable of exciting the changes set up in specific processes, is present.

Elsewhere I have indicated that it is necessary to study the epithelial tissues and the connective tissue separately, in order that we may be able to gain some insight into their relation to tumour growth.

All epithelial surfaces are covered with a single layer or with several layers of cells, the forms of these cells varying very considerably according to the function that is assigned to them; in fact, they can only become fully developed as the necessity for some special function comes into play. Whatever epithelial cells we examine, and in whatever conditions, it may be accepted that the greater their vegetative power the less completely is their functional activity developed. We have an exceedingly good example of this in what takes place in the embryo, where, development and growth going on rapidly, the cells are called upon to exert little or no function, and no draft is made on their energy and nutrition for carrying on of such function, the whole of these being therefore devoted to reproduction. At the same time the connective tissue cells are extremely active, although they in turn do not become fully developed, as we see from the mucous tissue that is found as the forerunner of the subcutaneous areolar tissue. It is during this period that all the infoldings of the epithelium that take place in the foetal tissues occur. We have the scaffolding of the whole gland erected long before it is called upon to perform any function, whilst in the developing mammary gland of the adult, when it first becomes active, the initial draft on its resources is in connection with an active proliferation of the cells of the gland acini, and is not associated directly with any functional activity. During this period of development of the embryo within the uterus, and of the breast at puberty, we cannot describe either of the groups of tissues as being in a *stable condition*, and we can readily imagine that any great nutritive disturbance, especially when this impairment is due to increased demand on the cells, due to local irritation, may result in tumour growth.

Why do we get the age distribution of tumours that was insisted upon, now many years ago, by Virchow and Paget? Why are sarcomatous tumours so much more common during foetal and early life than in old people? Why are the tumours of adult life, those which have no great tendency to become malignant—adenomas, cystic glandular tumours, fibroid adenomas, or cystic sarcomas, in which we have always an increase in both sets of tissues, and which vary in one direction or another, becoming more sarcomatous or more glandular, according to the age at which they are developed? Why are epitheliomas, as a rule, met with in old age, or rather at the end of adult life? May it not be that similar stimulating or irritating agents are capable of giving rise at different periods of life to these different forms of tumours, and that the essential difference consists in the different nutrient and developmental conditions of the tissues?

I shall have something to say against this theory, but for

the present let us look at it as affording some explanation of the occurrence of different tumours at different periods of life. In the embryo and during the first years of growth we have as yet an unbalanced condition of the tissues, the building-up process in which the connective tissues are specially concerned is going on at a great rate, and tumours occur in those tissues—the connective tissues—on which the greatest strain is put under ordinary developmental conditions, and which therefore are, as it were, in a condition of unstable equilibrium; a comparatively slight increased stimulation being sufficient to maintain the vegetative activity at the expense of the true connective tissue-forming power. In adult life, as has been frequently pointed out, the two sets of tissue may be looked upon as growing equally side by side; they are now both past the great vegetative strain, the connective tissue framework has been completed, the functionally active gland cells have taken their position and part in the economy of the tissues, and both sets have settled down to their everyday work and to their everyday nutrition: the nutrition and function of the one appearing to be dependent in a very marked degree on those of the other. An increased growth of the one is accompanied by a similar growth of the other, and in both cases the cells are so far stable that their vegetative activity is never excessive. Local irritation or increased blood supply may set up a localised hypertrophy, as it were; but beyond this we have no tendency to the formation of malignant tumours.

During the period at which cancer is usually developed, but when, of course, sarcomatous tumours may also occur, the connective tissues have passed their prime. The epithelial tissues have also reached their zenith, and are now on the turn; but, as we know, they have still great vitality, sufficient, indeed, when diverted from the imperfect functional to a vegetative activity, to give rise to very large masses of imperfectly-developed epithelial cells which, as in the embryo, appear to have the power of invading the connective tissue.

That this is not a fanciful idea anyone who has watched the healing of an ulcer will at once understand, for at the margin where the epithelium is proliferating actively and covering in the granulation or embryonic connective tissue, large processes or masses of epithelium may be seen pushing their way down into any little spaces not perfectly filled up by the granulation tissue, and in some cases, apparently, even entering for a short distance the provisional lymphatic spaces between the loops of granulation tissue covered vessels. In the epithelial tumours—such as cancer of the breast—which occur at the physiological decline of life, especially in women from 45 to 50 years of age, at that period (as Paget points out) when the functional activity of the highly organised epithelial tissues of the milk gland is declining, this great proliferative activity under stimulation is well seen. If the stimulation of these gland cells is continued there is necessarily an increased demand on their activity, and they, although unable to perform their full function, have still within them great powers of vegetation, and as a result we have a number of imperfectly developed epithelial cells.

I have long been of the opinion that in classifying cancers, and epitheliomas, the age of the patient is not the only factor that has to be taken into account; the organ affected must also be taken into consideration. We know that epithelioma of the skin and mucous membrane—tissue in which function is never highly specialised, but which remains longer than in the more specialised glandular cells—is usually developed later in life than cancers of the uterus and breast in which the function is lost at a comparatively early age. Epitheliomas, for instance, are probably commoner between the ages of 60 and 70 than at any other period.

Some time ago I examined a series of tongues taken from patients of different ages, and afterwards Dr. T. W. Dewar continued the investigation of the changes that take place in the epithelial tissues in a large number of tongues taken from patients at various periods of life. As the result of this examination I should like to bring under your notice several important facts which, up to the present, have not been systematically studied. I wish simply to point out certain structural peculiarities of an investing epithelium taken from a definite point at different periods of life, and to insist upon the importance of these differences in connection with the etiology of cancerous growths.

As we advance in life the epithelial covering of the tongue—at first a very thin, delicate layer—becomes a more and more important feature. In an eight-months' fœtus—a specimen of which I throw on the screen—the epithelium of the side of the tongue consists of several layers of cubical cells covered by one or two layers of slightly flattened cells; the papillæ are few and small, and the sub-mucous tissue is distinctly myxomatous. Here already a certain balance is maintained, for although the connective tissue is extremely delicate, and is apparently growing rapidly, there appears to be no very great activity of the epithelium, which forms merely a thin delicate covering; it is exposed to little or no irritation, and has no tendency to invade the connective tissue. In the tongue of a child two or three years old, we have a very different state of affairs; the sub-epithelial tissue, although still growing rapidly as is evident from the large number of nuclei to be seen, has now a more definite connective tissue structure, the vessels are well developed and large, and the epithelial cells on the surface have a characteristic arrangement and appearance, the cells of the germinal layer are cubical or slightly columnar, those above the columnar cells are polygonal, and those near the surface are flattened and often of considerable size. In the adult, where as we have seen, we reach a condition of equilibrium, the connective tissue, though increased in quantity, contains fewer small round cells, although the blood vessels are still numerous and well developed; the epithelial layer is simply thicker and the horny layer is rather more distinctly marked. On examining the tongue of an old person it is at once evident that both the connective tissue and the epithelium have undergone very marked changes; the sub-epithelial tissue is distinctly less in amount, whilst here and there are groups of small round cells; the fibrils of the connective tissue are wider apart and appear to be considerably atrophied. The epithelial covering on the other hand has assumed a very different appearance; the masses of cells, instead of being simple, as in all the specimens examined up to the present, are more or less ramified, small finger-like processes passing down from the main column into the connective tissue spaces, until in some cases one might almost imagine that we were examining an epithelioma, especially where there are small cell-nests formed in the thickened epithelium. When this condition of affairs is normally present—for such a condition appears to be present in the tongues of most old people—it is easy to understand how some comparatively slight, but long continued irritation at this point may give rise to an epithelioma; we have practically an invasion of the much atrophied and non-resistant connective tissue by the highly vegetative epithelium. Similarly in old people it has often been remarked that as involution of the breast proceeds the connective tissue becomes opener, the spaces larger and the cells fewer; in fact it becomes atrophied, and this atrophy becomes more marked as age advances. If during this period of atrophy there is no irritation, there comes a time at which the epithelium also undergoes atrophic changes, and there is a steady involution. Should there be any irritation, however, instability of the epithelial cells results; we have proliferative activity of these cells, an invasion of the non-resistant atrophied connective tissue, and the formation of a cancer.

In speaking of the anarchy produced in the epithelial cell, Mr. Marshall gave as his evidence of this condition the fact that he had observed that in certain cases, at any rate, the secretion, if such it may be called, of a glandular cancer gave an acid reaction. Working this single point out, Mr. D'Arcy Power has been able to demonstrate that the reaction given by the scirrhus carcinoma to test paper is almost invariably alkaline, and that therefore we have at present no data on which to base the theory that carcinomata can owe their infective properties to any definite radical alteration in the cell secretion of their epithelium. I have repeated these observations from time to time in a very large number of cases, and I perfectly agree with Mr. Power on this point, as only in one or two cases in which there had evidently been an accumulation of secretion near the surface, and from which, therefore, it was not possible to exclude fermentation processes, was there any acid reaction. For this purpose it is not even necessary to have a delicate test, the alkalinity being usually so marked that it may be determined by the use of almost any of the ordinary test papers.

Another very important factor recently brought out is, that apparently it is not necessary that there should be direct continuity of protoplasm between a nerve and a cell in order that the cell may be influenced or controlled by the nerve; in the central nervous system it has been demonstrated that there is a kind of process of induction by which a current sent through fibres in close proximity to the cell appears to set up a kind of induction influence on the protoplasm of the cell; and although this has never yet been worked out in connection with the peripheral end of nerves, it is a subject well worthy of being studied, and one which should repay very prolonged investigation. Cells may certainly in this way remain under the controlling influence of nerves as long as there is no excessive irritation, but we can scarcely imagine that in the case of a tuberculous granulation, for instance, such control remains, and that nerve fibres remain in sufficiently close proximity to the proliferating cells to exert any control over their further development. Here we have outside agencies—in this case the tubercle bacillus and its excretions—exerting a much more powerful influence than any direct or induced nerve-controlling power. Sir George Humphry, writing on macrodactyl, maintains that the increased size of a part may be attributable to a purely local stimulus, and he indicates that in certain conditions where we have localised growths to begin with, these may take on a malignant character; he says "localised overgrowths of the respective tissues started into activity by some unknown cause." He takes as an example simple warts which, as we know, frequently become warty epitheliomas, and eventually infiltrating epitheliomas. What is the essential difference between an epithelial growth which we speak of as a wart and a true epithelioma? We have the same elements present in both; we have an excess of epithelium and a more rapid proliferation of the connective tissue papillæ with its vascular and lymphatic supply, as compared with the normal skin. If this growth appears in the child, it is as a rule merely a temporary growth which disappears when the irritation, whatever be its character, is removed. Even if it continues for a number of years, it remains simple in its nature, and is in no sense malignant. A mole occurring in an adult may pass through exactly the same series of changes, and it is only when the period comes during which there is a disturbance of the balance of the tissues—that is, of the *stable condition*—that a malignant growth sets in. It may be objected that as yet we know little of the laws that regulate normal growth and nutrition, but we have certain observed facts which at least give us indications as to the nature of some of the processes observed in the evolution of cancer.

It may be accepted for the present, then, that malignant tumours are to be looked upon as overgrowths of certain tissues started into activity by some unknown cause. This unknown cause has been a subject on which the pathologist has bestowed the most earnest attention since the existence of tumours was first recognised, and abstract philosophers seem to have been as assiduous as scientific observers in their efforts to find this cause. It has been recognised that it is necessary to search beyond the condition of the tissues themselves for a primary causal factor such as would account for the peculiar proliferation of different sets of cells under definite conditions and at certain periods of life. Mechanical, chemical, and vital stimulation each in turn has been called upon to play its part, and each in turn has been cast aside or has been accepted as playing but a partial rôle. It has been found that malignant tumours of an epithelial type cannot be produced in healthy tissues, although certain adenomatous forms have been ascribed to the action of irritants on comparatively healthy tissues. It has also been indicated that if the irritation that brings about this formation of simple tumours be continued for a considerable period, or if during the process of irritation a "cancerous age" is reached, a cancerous element, that is, rapid vegetative power of the epithelium leading to invasion of the lymphatics, is developed.

What, then, can be the exciting cause of cancer formation? We have already spoken of the unbalanced condition of the tissues and of the vulnerability to invasion of connective tissues by epithelial cells under certain irritative conditions and at certain ages, a vulnerability first indicated by Thiersch. For the development of cancer it is necessary

that there should be a continuous irritation, and one capable of multiplication. Hitherto in the examination of irritants few have been found that have the power of keeping up continuous irritation for any length of time: such as have been met with are confined almost entirely to those vegetable parasites that specially affect the connective tissues. Many parasitic vegetable organisms have been found affecting such tissues, but up to the present comparatively few have been found that have the faculty of living in any of the active epithelial cells of an animal. So markedly is this the case that epithelial cells are usually described as offering a most determined resistance to the entrance of most vegetable micro-organisms.

After the demonstration of the fact that bacteria were capable of setting up proliferative changes in the connective tissues, great efforts were, very naturally, made to determine whether similar organisms might not play an equally important part in setting up cancerous proliferation, and numerous observers, working with more zeal than accuracy or knowledge, thought that they had succeeded in demonstrating the presence of specific vegetable micro-organisms in epithelial growths. These, however, in most cases, have been proved to be merely common saprophytic organisms. We can, of course, readily understand that micro-organisms have been found, when we remember that already there have been described more than 100 of these vegetable parasites as occurring on cutaneous surfaces, and it would be very extraordinary indeed if none of them found their way into some part or other of cancerous tumours. As pointed out by Verneuil and others, these organisms may play an important secondary part in setting up fermentation of cutaneous secretions, and in inducing inflammation of the connective tissues, or in breaking down imperfectly developed tissues, but up to the present we have absolutely no warrant for saying that they do anything beyond setting up those changes which may lead to softening and ulceration of the tumour. We are then compelled to look elsewhere for an exciting agent, an agent which must act continuously in the sense that it has the power not only of persisting, but of increasing in quantity and in activity. It must also have, under certain conditions, the power of acting almost specifically on epithelial cells, and of setting up proliferation in them at the expense of their functional power. All these qualities must be inherent in the irritant that has the faculty of stimulating epithelium into cancerous activity; this we know from our observations on the nature of the disease. It is here not necessary to go into the history of the earlier observations (which, though comparatively recent, are now classical in the truest sense of the word), carried on by Paget, Darier, Wickham (on Paget's disease), and others. I have time merely to deal with some of the more important facts that indicate the lines on which future work must be carried out in connection with the etiology of cancerous growths.

It has long been known to zoologists, especially to those interested in the animal parasites (Davaine, Leuckhart, Eimer, Kloss, Balbiani, Lieberkühn, Waldenburg, Rivolta, and many others) that we have a number of parasites, most of which affect epithelial cells, which exhibit little motion, are more or less homogeneous in structure, but which are surrounded by a hard smooth cuticle. This class of organism has been specially described as occurring in the liver of the rabbit, where, under the name *coccidium*, it is known to set up a peculiar irritated condition of the bile ducts, which ends in the formation of psorosperm nodules, which are really cysts containing papilliform projections covered with rapidly proliferating epithelium in the cells of which are numerous protoplasmic bodies, answering in all respects to the description above given. Similar organisms, setting up similar proliferative changes, have been described as present in the epithelial cells lining the intestine of the mouse, the dog, cat, rabbit, and even of man; whilst in the pike, the snail, and others of the lower animal organisms they are met with in considerable numbers in the epithelial cells of various parts of the body. On examining the literature and descriptions given of these parasites, and of the effects they produce, one cannot but be struck by the very marked similarity, not only as regards the naked-eye appearances, but also as to the histological changes generally (especially those that are found in the epithelium), between

psorosperm nodules and cancerous growths. I have already mentioned the nature of the growths found in the liver of the rabbit, and I find that one or two interesting cases of coccidial infection have been recorded as occurring in man. Leuckhart, describing a case mentioned by Gubler of Paris, points out that what he thought was due to the presence of the egg of a *distoma*, was really due to coccidial infection:—A patient suffering from disordered digestion, bad appetite, acid stomach, and anæmia, had an enlarged liver, from which projected a spherical tumour; this was diagnosed as a hydatid cyst. There was great anæmia, accompanied by cachexia, violent pain, great fever, feeble pulse, vomiting of bile, and collapse. On *post-mortem* examination there were found in the enlarged liver about a score of cancerous-looking tumours from the size of a chestnut to 5 inches in diameter; within these were found coccidia embedded in or near the epithelium, which was undergoing very rapid and extensive proliferative changes. Here we have a case of multiple tumour formation in which epithelial proliferation was one of the main characteristics, whilst it was accompanied by a marked cachexia. I have already stated that the cells of the intestine are also invaded by these coccidia, and that when so invaded they become subject to great epithelial proliferation; this has been observed in rabbits, dogs, cats, sheep, pigs, guinea-pigs, and moles, whilst fowls, ducks and geese, according to Rivolta and Zürn, are also affected in a similar fashion. Virchow and Eimer describe similar conditions in the intestine of the human being in which the epithelium of the intestine, first proliferating, was afterwards for the most part riddled and destroyed by psorosperms.

We have here, then, in the lower animals, organisms which, as parasites of the epithelial tissues, set up and maintain continuous proliferation, and comply with all the conditions required, theoretically, in the irritant that should be the cause of cancer. This being the case, it was natural that in psorosperm infection observers should look for the cause of epithelial cancers, and for long there has been a vigorous strife between those who believe that certain structures met with in the epithelial cells are merely colloid bodies, and those who maintain that some of them at least are parasitic organisms which have a definite structure and play a definite part in the production of cancerous growths.

There is no doubt that the question to be solved is one of extreme difficulty, and one, also, which will take us only one step nearer to a clearing up of the whole subject. It is rather a curious fact that nearly all the earlier observations as to the presence of coccidia and psorosperms in epithelial structure were made before staining methods were much used; indeed, such staining methods as have been used to within the last few years appear rather to have led observers astray than to have given them any very definite help; as the outcome of the use of the most recent hardening and staining reagents and methods, however, more and more light has gradually been thrown on the nature of these mysterious bodies. First of all, eosine and logwood were used to obtain a differential stain of the organism as it lay embedded in epithelial cell, and up to the time that Russell's paper appeared these reagents were the great stand-by of those who believed they were able to demonstrate the presence of coccidia in epithelial growths. Then came Russell's paper, in which he pointed out that he could stain certain structures very brilliantly, structures which appeared to affect specially the epithelial cells of cancer, and which to him appeared to bear a definite causal relation to the growth of cancer, which were apparently more numerous where the tumour was growing rapidly, and that in some at least he was able to distinguish traces of structural differentiation.

With the assistance of Mr. Douglas Stanley, M.B., I have been able to examine a very large number of tumours kindly supplied to me by Mr. Hulke, and have so been able to confirm Russell's observations as regards the presence of his so-called fuchsin bodies. There is, however, a great drawback to the fuchsin method. In specimens where the fuchsin bodies come out most brilliantly, and where most other tissues are decolorised or stained by the contrast stain, a few red blood corpuscles retain the red stain very tenaciously; there are also a number of free fuchsin bodies, the nature of which it is impossible to make out, as they are absolutely

structureless. It may be that some of these are developmental forms of the larger fuchsin bodies, but some of them resemble the small granular or homogeneous globules which appear to be the result of degenerative processes in the epithelial cells. It would, however, be unwise for one to commit one's self absolutely as to the nature of these globules.

Russell looks upon these fuchsin bodies as being probably somewhat closely related to the yeasts, and he describes in them a kind of reproduction by budding, which he thinks supports his contention. On careful examination of many specimens, specially hardened with bichloride of mercury and alcohol, I was, however, led to believe that these bodies resembled the coccidia group more than any other known organism; in the larger ones, especially, where there appears to be a distinct investing capsule, there is often a rather more deeply stained centre, sometimes granular, sometimes perfectly homogeneous, whilst the differentiation between the central portion and the periphery is frequently well marked, the central portion being irregularly mottled with small radiating projections, which may be either sharp-pointed or club-shaped. Again, the protoplasm within the capsule sometimes assumes a stellate form. Wherever these larger organisms are found small fuchsin-stained points can always be distinguished in or near the nucleus of the proliferating epithelial cells; they are quite distinct from the nucleus, and the only thing to which they can be compared is the adnuclear body. In some cases the nucleus is pushed to one side, forming a crescent around one end of the fuchsin body, whilst in other cases the nucleus has almost disappeared, and the fuchsin body appeared to be surrounded by a ring of protoplasm—the remains of the epithelial cell—with a little granular matter—the remains of the nucleus—at one corner. Soudakewitch's observations, recently announced in the *Annales de l'Institut Pasteur*, offer most important confirmatory evidence as to the nature of these intracellular organisms—important because he has been able to demonstrate the possibility of throwing these objects into much greater relief than has ever yet been done. On account of the thick chitinous capsule of the coccidium its contained protoplasm appears to be little affected by the action of weak chromic acid or Müller's fluid, and the organism continues to live and then to undergo degenerative changes after the protoplasm of the epithelial cells has been partially fixed by the hardening reagents. By fixing the tissues rapidly with bichloride of mercury, osmic acid, Fleming's solution, or absolute alcohol, the structure of these organisms is retained, in some degree at any rate, and then, by staining with logwood or with logwood and safranin, this structure can be brought out fairly distinctly. After examining specimens so prepared, so great an authority on zoology as Metschnikoff pronounces the organisms to be undoubtedly coccidia. Soudakewitch tells us that he had examined by the older method fifty-nine cases of cancer before he tried the newer methods, and in the whole of them he had found intracellular bodies similar to those already described, and which he concluded were probably coccidia. Since then he has examined a considerable number of cases, and he states that he has been able to demonstrate psorozoa in every one of ninety-eight cases of cancer that he has examined.

Dr. Ruffer and Mr. J. H. Walker have placed at my disposal a number of sections, stained with a combination of aniline dyes, some of which are under the microscope, others we have been able to photograph under a magnification of 800 diameters, whilst accurate drawings of others have been made by Mrs. Ruffer. A careful examination of these sections removes all doubt as to the nature of these bodies; they are certainly not the result of degenerative processes; they are not leucocytes or red blood corpuscles taken into the epithelial cells, though small cells appear to find their way into the proliferating epithelial cells in some cases; equally certain is it that they are not vacuoles. They have indeed, as Metschnikoff points out, all the characters of coccidia. In some of the capsules there appears to be a process of division going on, whilst here and there are capsules in which several (4 to 12) small, rounded, or crescent shaped psorosperms, in other respects like the coccidia except that they have no capsule, may be made out. In one or two instances these appear to be lying free between the epithelial cells, from which they have probably escaped on the breaking down of the mother

capsule. They are of very various sizes, from the diameter of a red blood corpuscle to three or four times that size.

On examining a section of a rapidly growing secondary cancer in which these bodies are present, the proliferation of the epithelium is always most marked where the encapsulated bodies are most numerous. In the larger alveoli many of the cells contain these organisms, and in the long narrow spaces where we have simply a single row of epithelial cells, every third or fourth cell may be seen to contain at least one, whilst in transverse sections of these spaces a single one of these bodies fills up the whole of the cavity.

In nearly 200 cancers not specially stained, and examining them after I had seen the fuchsin stained bodies, I have found bodies many of which closely resemble coccidia, and I have come to the conclusion that much of the difference of opinion that exists as to the nature of these homogeneous looking bodies is due to the fact that different observers have examined perfectly different tumours from different sites, some taking those that have grown very rapidly, others examining tumours in which the process of vegetation has been proceeding but tardily. There can be no doubt that coccidia are comparatively scarce in certain slowly growing primary tumours occurring on free surfaces, in which colloid or horny matter is present in very considerable quantities. In rapidly growing cancers, especially in secondary cancers and those that occur in women between the age of 40 and 50, they are, on the other hand, very numerous.

We are still, however, very far from having proof that these organisms are the actual cause of cancer. Why should they make themselves felt only under certain conditions and at certain periods of life? We have already spoken of some of the conditions favourable to the production of cancer, and it may be, as Mr. Jonathan Hutchinson says in respect to the production of tubercle by the tubercle bacillus, that a special kind of soil, and one to which special kinds of manure have been added, is required for the nutrition of the psorosperms. The conditions of parasitism are such that the healthy dry epithelial tissues are enabled to resist the attacks of even the most vigorous parasite; when once, however, their functional activity is impaired or their vitality somewhat lowered, the coccidia may find a nidus in which they may develop, secrete the products of their protoplasm, and so act on the epithelial cells, giving rise to proliferation by never allowing them to become fully developed, and thus by their irritation bringing them back to their embryonic form, during which their vegetative activity is increased in proportion to the impairment of their functional activity; it is this vegetative activity that enables them to invade the lymph spaces of the connective tissue.

Beyond this, however, these same products of metabolism must exert an irritant effect on the connective tissue in the immediate neighbourhood of the proliferating epithelial cells, and so give rise to what is practically granulation tissue; the greater the departure of this from the normal fully-developed connective tissue the more readily does it allow of the invasion of the proliferating epithelial cells. May not these secretions also play an important part in the cachexia which is so marked a feature not only in cancer but in all cases of coccidial disease, both in man and in animals?

One extremely weak link in the chain of evidence is that hitherto all inoculation experiments with cancerous material have failed, most signally, to produce any cancerous reaction. At first sight this appears to be an almost insurmountable obstacle to the acceptance of coccidia as the primary causal agent in the production of cancer; but it must be remembered that the evidence offered by zoologists as to the nature of these organisms indicates that they are exceedingly fastidious, both as to the positions in which they will grow and the kind of nutriment they will take up. For example, quite distinct forms of coccidia are present in the epithelium of the intestine and of the liver of different animals; we have one form in the liver of a rabbit, another in the intestine of the mouse, a third in the renal organ of the snail, and a fourth in the skin of the fowl; but all appear to affect specially the epithelial structures, more especially the nucleus of the epithelial cell.

In the inoculation experiments that have been made, the cancerous mass has usually been introduced into the connective tissue, into the veins, or into the abdominal cavity, in which position, although it has been demonstrated that

coccidia can retain their vitality for three days, the tissues in which they are lodged, and eventually the coccidia themselves, are absorbed by the new connective tissue that is formed around them, a small mass of such connective tissue being all that is left to indicate the locality of the inoculated tissue. As soon as the epithelial cells disappear, the coccidia have nothing on which they can subsist or in which they can grow, and they immediately undergo degenerative changes, and are removed just as were the epithelial cells. Even under the most favourable conditions for their growth and development they appear to be able to continue their existence only when protected from the connective tissue by the proliferating epithelium in which they are lodged. It is little wonder, therefore, that inoculation experiments have not succeeded. They have been done on animals with healthy resistant tissues; as a rule they have been from man to animals, and our attempt to cultivate these exceedingly delicate organisms on highly resistant connective tissues—tissues which under ordinary conditions they seldom affect—have failed most signally. Some more recent experiments have been carried out in which these facts have been kept in view, but as yet no definite results have been obtained. Any future experiments must be made with organisms cultivated outside the body, and they must be introduced or kept in position on epithelial surfaces, where they may have some chance of going through part of their life-history under normal conditions. It will be necessary to try these inoculations on different species of animals and on individual species at all periods of their life-history; only by doing this is there any chance of our being able to arrive at any further conclusions. Another point to be considered is one arising out of the fact that these organisms, which are so frequently found in cancerous tumours, do not necessarily pass through the whole stage of their life-history in the epithelial cells. It is known that in the case of the rabbit, psorosperms pass from the bile duct into the intestine, and so into the faeces, whence they reach the outer world. Under certain conditions of moisture and heat, coccidia form psorosperms—the small, more delicate forms—within the original capsule; the capsules burst, and the organisms may be taken again into the alimentary canal. Feeding experiments carried on by Leuckhart, Eimer, and others, have all gone to prove this, so that the question of the endemic nature of cancer, if it is proved that these coccidia are its cause, will have to be gone into more carefully than was at one time thought necessary. Hirsch entirely pooh-poohs the idea that climatic influence and state of the soil can have anything to do with the comparative frequency of cancer in certain districts. Haviland, however, maintains that in England cancer is least prevalent on rocky ground and high-lying places, and most common in marshy regions and on the wet soil of river basins subject to inundations. The conditions present in these localities described by Haviland are exactly those necessary for the development of the psorosperms of rabbits, a disease which is always most frequently met with amongst rabbits whose run is over marshy ground or over narrow areas where the drainage is imperfect. Even the examples that Hirsch gives as controverting Haviland's arguments are not at all conclusive, for as he admits even in Norway, where cancer occurs mostly in the mountainous districts and at considerable elevations, it is also met with along the fiords in the low-lying country, and not near the open coasts, where the drainage is invariably better than in any other part; whilst even on the high tablelands of Mexico, which are more subject to cancer than the plains, we have no information as to the conditions of drainage, and therefore no accurate information on which to base any argument.

A coccidial origin of cancer, if proved to be correct, would render it necessary that we should throw aside the doctrine that cancerous epithelium can be developed from anything but epithelial cells. We can, no doubt, find various kinds of epithelium, according to the seat of origin of the cancer, the rapidity with which the cells proliferate, and the extent of the invasion; but in every case we find epithelium which resembles, in a greater or less degree, normal epithelium. From what has already been said as to the relation of the coccidium to the epithelial cell, it is evident that, in order that a primary cancer may be developed or a secondary cancer grow, epithelium must be present in which the coccidium can maintain its existence and perform its parasitic functions.

In the first place a primary cancer must have its origin at some sitewhere epithelium is already present, and at some position to which the coccidia may make their way from the exterior of the body. In the case of the secondary growths, which, as we know, occur in positions in which no epithelium is normally present, we must have the coccidia brought from the primary source of origin of the tumour. This, as we have seen, can probably take place only when the organism is protected by an epithelial cell; and the epithelial cell which contains the organism is the parent from which future generations of cancer cells may be developed.

I should here like to go much more fully into some of these points; but my time is now short, and, before I conclude, I wish to say a few words under my third head.

In all our researches as to the nature and etiology of cancer, we have in view the alleviation of the suffering of those who are affected by this disease; and hitherto our main object has been to determine how far it was necessary to remove certain structures in order to minimise as far as possible the chance of any return of the disease. From a careful microscopical investigation of many hundreds of cancers that have been submitted to me for examination, I am firmly of the opinion that many surgeons make the mistake of not removing sufficiently freely either the tissues in which a cancerous growth has made its appearance or the lymphatic glands associated with the organ in which the cancer is developed. Quite recently Mr. Harold Stiles (of Edinburgh) has carried on an extensive and careful investigation into the question of how far the immediate tissues around the naked-eye cancer of the breast are affected; and at a meeting of the Edinburgh Medico-Chirurgical Society held in the early part of this year he demonstrated a method that he has had in use for some time, and the results of which I have frequently had the opportunity of examining, of determining within a very short time of the removal of the tumour and without microscopical examination whether the whole of the glandular tissue around a cancer, or even the cancerous tissue itself, has been removed or not. Working with Mr. Brooke in the Embryological Laboratory at the University of Edinburgh, he placed thin slices about $\frac{1}{4}$ -in. in thickness, taken from the margins of the tumour, for a few hours in a mixture of 5 parts of nitric acid in 100 of methylated spirit. If the sections are more than $\frac{1}{4}$ -in. thick they are left for a longer time. They are then plunged into water. He found that the nitric acid so changed the tissues, that when the section was immersed in water even for a few minutes the connective tissue began to swell up, whilst the masses of epithelial tissue remained perfectly opaque; in this way he was able to see at a glance whether the epithelial tissue extended to the margin of the removed growth or not, and whether the columns of epithelium were like those met with in an ordinary gland. From a careful study of sections so prepared, both by Mr. Stiles and myself, as well as from microscopic examination, and from what I have seen of the work of Mr. Beadles and Mr. Raymond Johnson, I firmly believe that those surgeons are in the right who maintain that the only safe rule to be observed in removing cancer of the breast is to remove not only the main mass of the gland but all outlying portions of glandular tissue, both laterally and in depth, so that if on cutting away the margins of the tumour, treating with the spirit and nitric acid and then with water, any opaque columns or fragments are still to be seen, I should consider that the removal has not been free enough. Of course, the part of the tumour that should be specially examined in such a case is that near the sternum, where, on account of the shape of the incision usually adopted, as pointed out by the late Charles Moore, and mentioned to me by Mr. Hulke, there is the greatest danger of fragments of the gland being left.

Elsewhere I have indicated that we have ample evidence that where there is increased metabolic change in any special set of tissues, or wherever we have any irritative material acting on the tissues of a certain area, or where there arises the necessity for the removal of foreign or effete material, there we find, developed along the course of the lymphatic channels, small masses of adenoid tissue which act as filters or transformers, the active amoeboid cells taking up and breaking down not only particulate matter, but also many of the chemical substances brought to them.

It happens, therefore, that in cancer of the breast, where we

have active metabolic change going on as the result of the action of the exciting cause of cancer upon the epithelial cells—for we are agreed that we can only look upon the cell activity as the result of some special stimulus—we have a much larger quantity of effete material passing from the breast, material which, because of its irritative nature, rapidly calls into play the development of this special filtration apparatus. That this is not purely theoretical is evident from the fact that every surgeon looks for enlarged glands when examining a cancerous patient; the best demonstration of the process is to be seen, however, as Stiles has pointed out, in the small lobules of fat that occur in the axilla; these small lobules, each supplied by a small vessel and its branches with the corresponding perivascular lymphatics, gradually assume a perfectly characteristic appearance. At the margin of the lobule, away from the entrance of the vessels, a few small cells are seen to accumulate; these form a kind of crescent, usually on the side away from the entrance of the vessel to the lobule. Gradually this line of cells becomes broader and broader, a delicate reticulum may be seen, and eventually the whole of the fat disappears, and we have a small cellular structure which in all its microscopical appearances resembles a small lymphatic gland. This has been demonstrated specially in the axilla, but a similar process takes place also in the connective tissue and fasciæ covering the pectoral muscles. These masses of cells, as we have said, appear to form transformers or filters for the chemical products of metabolism and for such other *débris* as has to be carried from the tumour by the lymphatic system. It is apparently in the network thus formed that the epithelial cells with their parasitic coccidia are intercepted; for it is here that the small secondary growths make their appearance, first in the glands covering the pectoral muscles, and also in some cases between the strands of the muscles, especially at their lower margin, and then in the lymphatics of the skin and glands in the axilla; not only in the glands that are normally present, but also in those that are formed as the result of the special requirements of the lymphatic system, in consequence of the growth of the cancerous tumour.

I shall not to-day attempt to enter into any discussion as to the relative frequency of the spread of cancer by blood vessels and by lymphatics, although latterly some doubt has been thrown on the accuracy of our present teaching in regard to this question. I will merely state that I am more and more convinced that cancer extends almost entirely by the lymphatic vessels, that this takes place not only locally by direct extension, but in some cases where the lymphatics are especially wide, and especially after they have been called upon to do temporary extra work, the cells may make their way for some distance without leaving any intermediate trace between themselves and the parent mass.

It may appear that I am taking much for granted, of which at present we have extremely insufficient proof, but I hold that until we have more definite knowledge on all these points, we must for the sake of our patients accept them as proved, and certainly take them into consideration when planning out our method of treatment, in which the main element must be free removal of the organ affected and of all those parts and structures—muscle, skin, lymphatic glands—between which and the original tumour there is any lymphatic (either perivascular or around ducts) communication, however imperfect under normal conditions this may be.

On going over the literature of cancer, one cannot but be struck by the extreme accuracy of the observations that have hitherto been made and recorded. They did not, when they were made, admit of any explanation, and many of them are still inexplicable, but we cannot but feel that by following up many of the older observations, and by gradually fitting them in to fill up gaps as new facts are accumulated and old or new theories proved, we may be able to obtain a fresh coign of vantage from which to start afresh, and at the same time often save ourselves much needless trouble. A recent novelist speaks of the track of the snow shoe as remaining invisible until spring comes round and the snow begins to melt. Then it begins to stand out, and remains as an evidence for some time after the untouched snow has disappeared that someone travelled that way during the dark and cold

winter months. So it is with all accurate and carefully-recorded observation. We may be sure that if our work is as thorough and as honest as that of the men who have preceded us, it also will take its place in the grand system of acquired knowledge that is being built up and buttressed now as it was not only fifty years ago, but in all preceding ages.

OBSERVATIONS ON THE COMPOSITION AND FLOW OF THE BILE IN MAN.

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IN vol. iii of the *Laboratory Reports* of the Royal College of Physicians of Edinburgh I published, in conjunction with Dr. J. Balfour, the results of a prolonged series of observations on the composition and flow of bile in a woman with a complete biliary fistula, which had resulted from an operation for the relief of jaundice produced by obstruction of the bile duct. The main conclusions arrived at were stated as follows:—

That the bile is to be regarded rather as an excretion than as a secretion playing any essential part in digestion. Although the liver undoubtedly develops primarily as a digestive gland, in adult life its relationships with the general metabolism are much more intimate than with the alimentary processes. All researches on the subject have clearly shown that the entrance of bile into the intestine is not essential for the maintenance of the individual in a perfectly healthy condition. The only digestive disturbance produced is the diminished absorption of fats; and, as we have already seen, there is good reason to believe that this is simply due to the withdrawal of a stimulant to the absorbing cells of the intestinal wall. But even with bile excluded from the intestine, no less than about 70 per cent. of the fats is still used. Again, all the constituents of the bile are bodies derived either from the decomposition of the red blood corpuscles—a process which is known to occur in the liver—or of these along with proteids from other sources. Of the pigments in this respect we need say nothing. Of the constituents of the bile acids it is sufficient to recall the fact that glycine and taurine are both amido-acids. In connection with the cholesterolin and lecithin there can be little doubt that these are derived from the stroma of the red corpuscles, since they form a by no means unimportant part of that stroma. The vague view that they are derived from the nervous system, taught by certain physiologists, is based upon no better evidence than the fact that both substances occur in these tissues. The absence of any direct proportion between the excretion of nitrogen and sulphur in the bile and in the urine—instituted on by Bunge—we do not think can be taken as disproving the connection of the biliary function, as well as the other functions of the liver, with the general metabolism. A careful study of the experiments of Kunkel and Spiro, upon which Bunge bases his conclusions, does show a more or less marked relationship; while the correspondence between the amount of bile solids produced and the amount of nitrogen excreted in the urine in our case strongly supports the view of their close connection. While health can be perfectly maintained when the bile is directed to the outside of the body, any interference with the general metabolism of the liver at once produces serious disturbances. And inasmuch as these are manifested by changes in the biliary secretion, the conclusion has been come to by physicians that these changes in the bile secretion are the cause and not the accompaniments of the disturbance. The undoubted beneficial action of the so-called cholagogues we believe to be due to their influence upon the general metabolism of the liver, and not specially upon its biliary function. This point one of us has dealt with more fully in a previous paper.¹

In support of these statements, I now give an account of the present condition of the patient, Mrs. W.

She left the infirmary for her home in March, 1891. At this time a short rigid tube in the fistula was attached, by means of a piece of flexible tubing, to a caoutchouc bag suspended at her side in a loop of bandage. The whole of the bile passed through the tube, rarely did any escape round the outside. During the whole period—from June, 1890, to the present date, March, 1892—every drop of bile has been poured out on the surface, and there has been no evidence that any has entered the duodenum. Nevertheless, her health and strength have steadily improved.

At my request, she visited me on February 22nd, 1892. I have never seen a more healthy-looking woman. Her complexion is clear and ruddy; her conjunctivæ perfectly clear; she is fat, and must weigh between eleven and twelve stone. She tells me that since her return home she has never had a day's illness, and that she is up every morning at her household work at five o'clock. She states that her appetite is very good, and that she can eat all kinds of food, even the most fatty, with perfect impunity. Her bowels move regularly once a

¹ BRITISH MEDICAL JOURNAL, 1886, vol. ii, p. 207.