RECENT RESEARCHES ON PROTOZOA AND DISEASE.

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MR. PRESIDENT AND GENTLEMEN,—In a few days, on October 16th, 1893, the 100th anniversary of the death of John Hunter will once more bring to our mind the memory of a man to whom all owe an earnest reverence. Although dead his spirit is transferred as a living activity to the Society which bears his name, and which is continuing the work of his life. Hunter was great because his genius applied the experimental method in physiology to the uses of surgery, and he devoted his life to experiment and to observation. We nowadays try to follow his methods, and by means of induction and experiment seek to unravel the many unsolved problems of physiology and pathology. It is of the results of observation that I intend to speak to-night, but whilst bringing before you the facts as they have been observed, I will try to remember what Hunter himself said: "Too much attention cannot be paid to facts, yet too many facts crowd the memory without advantage, any further than they lead us to establish principles." At the same time, I feel deeply the honour you have done me in asking me to give this Hunterian lecture, and, whilst thanking you, let me add that I have tried to follow Hunter's spirit by controlling, in collaboration with Dr. Plimmer, almost every fact of which I shall speak by direct observation.

I have chosen the subject of protozoa in disease as being one of the newest in pathology, but in the short time at my disposal I can touch on a very few points of this vast subject only. In order to save time I have omitted any reference to any workers on this subject, and I will add at once that I intend to give everyone his due when, as will shortly be the case, these notes and other observations are embodied in book form.

A few years only have elapsed since protozoa were first recognised as being the causative agents in a specific endemic disease, that is, malaria. Before that time their presence had been occasionally observed in both man and animals, but the fact attracted little attention until a French military surgeon proved that typical protozoa were to be found in every case of malaria. The same observer traced the life-history of this parasite, and although some of his interpretations have since been found to be incorrect, yet but little has been added to the actual facts which he published in his original papers. His observations and their interpretations raised a perfect storm of opposition; and, strangely enough, the leaders of it were the very scientists who, years afterwards, claimed the priority of his discovery. Since that time, however, the protozoon of malaria, which may be called the *hæmatophyllum malariae* (the name *plasmodium malariae* being hopelessly inaccurate) has been discovered by competent men in every country where malaria is endemic.

All attempts hitherto at cultivating it have been unsuccessful, nor has it yet been isolated from the soil or water of malarious districts. Our knowledge, therefore, is based only on examinations of blood taken from malarial patients, or of their organs after death.

This organism measures from 1μ to 10μ , but its shape is no doubt influenced by its habitat at the time of observation, as it is often flat and wedge-shaped when met with in the red blood corpuscles, and spherical when free. The organisms are as a rule naked; the semilunar forms alone, which are now regarded as conjugation forms, being surrounded by a membrane possessing a double contour, and which is not infrequently tinged with hæmoglobin. Each parasite possesses:

1. A nucleus and nucleolus; which latter, however, cannot be seen in the living protozoon.
2. A body, which is sometimes granular, and contains lightly refracting corpuscles; and which cannot be differentiated into an endosarc and ectosarc.
3. Protoplasmic processes.

The parasite is often vacuolated, and altered blood pigment (melanin particles) is suspended in its interior, this pigment being located chiefly at the periphery of the organism. When young the parasite does not contain any melanin corpuscles, but their presence can always be recognised after the disease has lasted one or two days. They are a product of the digestion and destruction of the red blood corpuscles by the protozoon, and represent in fact the fæces of the malaria parasite. The nucleus and nucleolus of the *hæmatophyllum malariae* never contain any pigment, and the nucleolus often disappears just before sporulation takes place.

The parasites are amoeboid, change their shape, and the contents (nucleus, melanin corpuscles) are often in active Brownian movement. The movements of the parasites are not powerful enough to produce locomotion; this is effected by means of the long whip-like processes, which vary in number from one to five, and the lashings and twistings of which among the red blood corpuscles in coverglass preparations are one of the most wonderful sights it is possible to witness with the microscope. The observer who has specially studied their formation is of opinion that they occur in all varieties of malaria, and that they enable the parasitic protozoa to adapt themselves to a saprophytic mode of existence. Some of the parasites may be actually in the red blood corpuscles, or else merely lying on them, or floating freely in the surrounding plasma. The infested blood corpuscle naturally enough does not thrive under such conditions; its hæmoglobin gradually becomes absorbed by the protozoon, and in the end the corpuscle disappears and nothing is left but an empty shell.

The multiplication is effected by simple division into a number of spores, with the formation of a well marked dead *noyau de reliquat*, which is afterwards deposited, under the form of pigment, in the spleen, liver, or some other organ. This process of division is best seen in patients suffering from quartan fever, and its extent varies somewhat in the different kinds of malaria. Another mode of reproduction may be studied in the pernicious forms of malaria, for, according to one author, the semilunar bodies met with in such fevers are formed by the conjugation of two such parasites, the fusion having been actually observed to take place under the microscope. The conjugation is followed by encystment and sporulation.

Later investigations have shown that, although the *hæmatophyllum malariae* is met with in every case of the disease, yet several kinds of it exist, and that the clinical manifestations of the malady are dependent on the presence and life-history of a specific parasite. These varieties may be divided as follows:—

1. Malaria parasites with sporulation and without semilunar bodies:
 - (a) Parasite of quartan fever.
 - (b) Parasite of tertian fever.
2. Malaria parasites with sporulation and formation of semilunar bodies:
 - (a) Pigmented parasite of quotidian fever.
 - (b) Unpigmented parasite of quotidian fever.
 - (c) Parasite of malignant tertian fever. (Mannaberg.)

We see, therefore, that there are probably as many varieties of protozoa as there are of pathogenic vegetable organisms.

A fact worthy of notice is that in many malarious places the birds inhabiting the district are infested by protozoa, which resemble in many respects those of malaria, and which are, in all probability, simply a variety of the same parasites. It is curious that these may be found in the bone marrow of birds when none can be discovered in the blood.

I have taken the *hæmatophyllum malariae* as the type of the protozoa which live in the plasma or red blood corpuscles, or, at any rate, multiply in the blood during some period of their existence; but, as you know, there are other protozoa which infest the tissues of the body, some preferring the muscles, some the connective tissue, others, again, the

nervous system, whilst a large number live in the epithelium cells. It is the latter class that we shall discuss to-day.

For pathological purposes, they may be divided into those which are not accompanied by a proliferation of the epithelium cells, and those which cause or are accompanied by such a proliferation. No doubt this classification is one which any zoologist would refuse to endorse; but let me ask you to accept it merely for the sake of illustrating my meaning.

We will take the *klossia helicina*, which inhabits the kidney of the snail, as the type of the first class of parasites. Its life-history is rather a complicated one. Shortly stated, the full-grown parasite encysts itself, and breaks up into a number of spores, in the interior of which falciform embryos ultimately develop. These spores burst, the liberated falciform embryos are then either voided with the secretion of the kidneys, or enter into another epithelium cell, grow into a mature animal, and go through the same cycle again. Of the symptoms presented by such snails, we know nothing, for obvious reasons. We have kept infected snails in the laboratory, and none of them died; and the kidney of a diseased snail could be distinguished from that of a healthy one through microscopical examination only. In order to settle the question as to whether the *klossia* produced any epithelial proliferation, serial sections were cut through the entire kidney. No sign of undue multiplication of cells was ever seen, even in the kidneys which contained the largest number of parasites. We noticed nothing to show that these gregarines produced any marked inflammatory lesion, and, in fact, we were astonished, to find a total absence of reaction on the part of the infected tissues. The only lesion which could be detected was that the infected cell elongates, gradually becomes detached, and falls into the lumen of the urinary tube. As the parasite grows, the cell is after a time reduced to a mere shell surrounding it. When the spores burst, the *débris* of the cell are simply excreted with the secretion of the kidney.

Another parasite which is apparently accompanied by little or no proliferation of epithelium is that seen after vaccination. Here I would speak reservedly. For I do not by any means endorse all that has been written as to the presence of parasitic protozoa in vaccinia. On the contrary, I believe that several authors have classed under that name many heterogeneous structures contained in the vaccinia and variola pustules; but that, on the other hand, these parasites have been seen by many, and have been correctly interpreted by one observer at least, and incorrectly by many others.

If one examines the epithelial cells at the point of inoculation of vaccinia forty-eight hours after this operation, one finds that the majority contain in their protoplasm round bodies, easily stainable with both nuclear and protoplasmic dyes. These are surrounded by a sharply limited clear space. They have no recognisable capsule, but lie quite free in the protoplasm, and with high powers of the microscope it is often possible to make out in their centre a spot which may perhaps be considered as their nucleus. These bodies multiply by fission and segmentation into two or multiples of two, and gradually invade the deeper layers of the epithelium, and even the connective tissue beneath. Their size varies, but as a rule it is constant, except just before division. They are many times larger than micrococci, but smaller than the parasites of cancer. On the third day many wander into the connective tissue, and some are taken up by leucocytes even before they leave the epithelium cells. Their ultimate fate, however, is uncertain, as on the fourth day the emigration of leucocytes is so great that, in the absence of well-marked staining reactions, we do not feel competent to distinguish them with certainty among the mass of leucocytes, necrotic *débris*, red blood corpuscles, micrococci, etc., which are found in the interior of a vaccine pustule. The same and other reasons prevent us from making any statements as to their number in vaccine kept outside the body, though such structures may be undoubtedly found in it. As has been seen from the above, these protozoa of vaccinia differ from the structures which we are to describe presently as the parasites of cancer in size, staining reactions, and structure, but they resemble them in the fact that they possess a similar mode of division. As to their pathogenic properties we know absolutely nothing.

The epithelium cells containing these parasites become larger, more spherical, oedematous in fact, and this hypertrophy of the cells causes the surface of the infected spot to become slightly raised. The cells are pressed against each other, and those which are partly invaginated look as if surrounded by a capsule, which in reality is the outline of the cell into which they are forced. They are, in fact, identical with the invaginated cells met with in cancer and erroneously described as parasites. Frequently, also, the nuclei undergo a process also seen in cancer cells, and which, for want of a better name, may be called the direct fragmentation of the nucleus, this direct fragmentation not being accompanied by division of the cell protoplasm.

On the other hand, indirect division, karyokinesis, although often met with near the point of inoculation, did not appear to us to be more prevalent there than near any other inflamed or irritated epithelial surface. In this case, therefore, as in the preceding one, we cannot conclude that the parasite gives rise to any marked proliferation of epithelium. This is practically all that we can say definitely about protozoa as they occur in vaccinia, for, up to the present moment, we have been unable to confirm any of the other statements made on this point, and those who have attempted to investigate this difficult problem will not blame us if we maintain a discreet silence as to the interpretation to be put on the structures met with in pure vaccine lymph. Some of them might fairly be considered as stages in the life-history of a protozoon; but, on the other hand, we have not been able to distinguish them from some of the constituents usually found in or near small subcutaneous abscesses.

Nevertheless, although we have no sure knowledge of the pathogenic properties of these parasites, although their life-history is but imperfectly known, there are several reasons, such as the failure of bacteriologists hitherto to isolate from vaccinia any micro-organism, which might be considered as the cause of the malady, the spread of the disease along certain epithelial surfaces, etc., which would lead us to believe that both vaccinia and variola are probably due not to a vegetable micro-organism, but to a protozoon. They would differ, however, from most affections caused by protozoa by the fact that in them one attack is protective against another, for a time at least, which is not usually the case in disease due to protozoa. I think it only fair to state that it was the remarkable work of Guarnieri (a copy of which was courteously sent me by the author) which caused us to reinvestigate this matter.

We may now turn to a protozoon which produces proliferation of epithelium cells, namely, the *coccidium oviforme*. This attacks rabbits chiefly, and gives rise to the small adenomata so frequently found in the liver of such animals. Its life-history is so well known that no account of it is necessary, but the disease produced by it is interesting because, clinically and pathologically speaking, it occupies a position intermediate between malaria and cancer. Like malaria, the disease is endemic in certain places, attacking nearly all the rabbits in a warren, or in a stable, and sometimes proving fatal to almost all the young animals. Its course is at first acute: the animals lose flesh, are attacked with diarrhoea, and die. At the *post-mortem* examination, the disease is localised in the alimentary tract and the liver. In the intestine, the foci are situated chiefly in the mucous membrane of the upper part of the intestine, and look to the naked eye like white irregular spots, which occupy at times most of the intestinal wall. In the liver, at this stage, they form small tumours situated in the bile ducts, and distending the same. These are filled with a thick creamy substance consisting of pus, epithelial cells, coccidia, etc., whilst the whole is surrounded by a capsule of fibrous tissue, sending branching prolongations into the interior of the tumour. The epithelium proliferates and lines each one of these prolongations. These are the appearances seen when the animal dies in the acute stage of the disease; but should it recover, the little tumours in the liver become encapsuled, and on section present all the appearance of a parasitic adenoma, each branching prolongation being surrounded by connective tissue, which encapsules it and isolates it from the remainder of the liver substance. In a later stage, the epithelium disappears by a process which will be explained later on, and the little tumour becomes a fibrous nodule. Here

then we have a disease which is caused by a protozoon, which may live in the epithelium cell, but which may also thrive even outside the cell in the body, and which produces an acute febrile disease, followed by a chronic process and accompanied by marked proliferation of epithelium cells.

The next point in my paper is the description of the structures, now considered by several pathologists and zoologists as protozoa, and which occur in all cases of cancer in man; but I am fully aware, and I warn you, that the interpretation which we put on such structures is not accepted by many pathologists.

The protozoa are found in the epithelium cells of carcinoma, and are round bodies, varying from 0.004μ to 0.04μ in diameter. They consist of a central part, or nucleus, which, as a rule, stains deeply with appropriate dyes. This is surrounded by a layer of protoplasm, which stains less deeply, and which, after the protozoon has attained a certain size, has a more or less radiated appearance. Surrounding the whole is a capsule. This capsule was at first thought to be secreted by the infected cell, as a kind of protecting membrane; but, on the other hand, it is no uncommon thing to find the capsule folded on itself. The protozoon may also be seen lying free in an alveolus, still surrounded by its capsule, so that the latter must be a part of the protozoon. The protoplasm of the protozoon is either quite homogeneous, or it contains a few granules, or the rays before referred to, which may be seen, in some cases, extending, both from the central part towards the periphery and from the periphery towards the centre. The nucleus is, as a rule, perfectly homogeneous, but, with the highest powers of the microscope, a lighter spot in the centre can sometimes be made out. The microchemical reactions of the nucleus of the protozoon are quite different to those of the nucleus of the cell, the principal point of difference being that the nucleus of the protozoon will not, as a rule, stain with the ordinary nuclear dyes. It is very difficult to get the nucleus of the protozoon stained with hæmatoxylin, or it shows the phenomenon of metachromatism. In sections stained with hæmatoxylin and cochineal the nucleus of the epithelial cell takes the hæmatoxylin, and that of the protozoon the cochineal. There are several other methods of showing these microchemical differences between the cell nucleus and that of the protozoon; the former, of course, staining with nuclear dyes, and the latter only with protoplasmic dyes.

Sometimes the granules I have mentioned will arrange themselves in a very regular radial manner close to the capsule, and the protozoon then resembles very closely the coccidia found in the rabbit's liver.

We have been able to demonstrate the method of reproduction in these protozoa. In the most frequent form the nucleus divides into two equal parts, being at first connected by very delicate threads, which disappear as the capsule divides, a septum being thrown out at each side and meeting at last in the middle, thus making two protozoa. This kind of division occurs most frequently in those protozoa which have attained a medium size. The other is of a more complex and rarer sort. The nuclear masses are arranged at the periphery of the sac, after the manner of the rosaces in malaria, and the capsule dividing septa are formed inwards which extend from the capsule between these masses. These gradually shut off the young parasites which are thus set free.

With regard to the presence of the parasites and karyokinesis, I would remark that, although the cells surrounding the infected one are often in a state of active proliferation, we have never seen a parasite in a dividing cell.

Let us now see whether there are any pathological facts which are common to all the diseases of this group. One of the most important facts concerning malaria and other diseases in which protozoa have been found, vaccinia excepted, is that when once the body has been attacked by them the parasites appear never to leave it again. Malaria may, as you know, recur even when the patient has for a long time not been in a malarious district. One example of this (observed by Dr. Plimmer and myself) will suffice. A gentleman of the highest intellectual distinction had been repeatedly attacked by malaria in India; he was invalided home, and for seven years was absolutely free

from the disease, and never went into a malarious district. He was staying with us in a house, the owner of which, a medical man, has inhabited it for many years, and in which no one has ever suffered from malaria. Going one evening through a dimly lighted passage he fell down a flight of stairs; he was picked up in my presence, and within five minutes had a typical fit of ague, and so well did he know the symptoms that he at once clamoured for quinine. Now where had the protozoon taken refuge during these seven years? We do not know what becomes of it in man during these long intervals of apparent rest, but the study of birds may throw some light on this, for, as has been seen, the parasites previously described in them are found encysted in the bone marrow even when none are to be found in the blood. These birds present no symptoms, as a rule, but sometimes the animal suddenly has distinct signs of illness, such as ruffling of the feathers, convulsions, and other nervous phenomena, the diseases being accompanied by the presence of protozoa in the blood. Moreover, the animal may have such an attack after it has been removed for some considerable time from a malaria district, and without any obvious reason for succumbing to the disease. I think we may argue, without any undue stretch of imagination, that in these birds, which have not been again exposed to infection, the disease is produced by a new crop of parasites which develop from those encysted in the bone marrow, and that a similar condition of things may exist in man.

The parasite of the snail also does not disappear when the animal is removed from the place where it has been infected. Through the kindness of Dr. L. Pfeiffer, of Weimar, we obtained a considerable number of living snails, in the kidneys of which we found a large number of typical klossia; about one in every three was thus infected. The animals were kept in the laboratory under a glass shade and fed with filter paper, but although the snails had thus been removed from their infected native place the parasites did not leave them, for on examining a number of them again, four months afterwards, we found the same proportion of infected animals.

The coccidium oviforme of the rabbit also may remain in the liver for an almost indefinite time without giving any further trouble. It is no uncommon occurrence to find in old rabbits small fibroid tumours, containing typical encapsuled coccidia, but whether these coccidia ever cause a new attack of the acute disease it is difficult to say, though, theoretically speaking, there is no valid reason why this should not occasionally take place. And, lastly, the recurrences of cancer are too well known to call for more than a passing reference.

These and other considerations lead me to believe that one disease, namely rabies, the cause of which has baffled even so great a genius as M. Pasteur, might perhaps be profitably investigated under the assumption that it is produced by a protozoon. Rabies differs from all bacterial diseases in that it possesses an indefinite latent period which, in man, is rarely less than three weeks, and sometimes extends to six years or more. No bacterial disease has a latent period approaching this in length, but on the other hand we have seen that pathogenic protozoa, both in man and animals, often remain latent for a considerable time, the disease breaking out often without any apparent reason. Why should not rabies be due to a similar protozoon? The fact that all attempts at cultivating its causative agent have failed, even when conducted by the best men under the best possible conditions, is strong evidence that the organism that produces rabies belongs to the animal kingdom. Also the fact that the virus of rabies is, to a great extent, localised, or at any rate is found in its most virulent form in one system of the body, and one which is but seldom affected by vegetable organisms, gives further support to the hypothesis that this disease may be caused by an animal parasite.

I now propose showing that the mode in which the organism reacts against the hæmatophyllum malarie, the coccidium oviforme, and the parasite of cancer, is practically the same in all these diseases.

In a drop of malarial blood one may watch under the microscope how the leucocytes absorb, kill, and digest the hæmatophyllum malarie; but whether this phagocytic process actually takes place in the circulatory system is a moot

point. Indeed, some maintain that it is limited to the macrophages of the spleen and bone marrow, which have been seen to destroy a large number of parasites after absorbing them, together with the red blood corpuscles. In the majority of cases the parasites are killed, but occasionally they destroy the macrophages.

One of the most competent observers has noticed that in quartan and tertian fevers the phagocytosis begins with the onset and lasts three or four hours longer than the actual attack. Later on the parasites are digested by the leucocytes, and the length of the attack may be estimated by the number of digested protozoa found in the preparations. It is possible, also, that the fever may actually cause the death of the parasites, though the evidence on this point is hardly sufficient to carry conviction.

In birds which are infected, the macrophages of the bone marrow destroy large numbers of the protozoa, and on transfusing blood from birds into frogs or dogs the leucocytes of the second animal have been seen to destroy the parasites contained in the blood of the first. The means of resistance of the organism against the parasite of malaria lies in the phagocytic properties of the mesoblastic cells of the blood and other parts of the body.

Now with the coccidium of the rabbit and the parasite of cancer the process is practically identical, but to prove this I must show that the stroma of the tumour is nothing more than the means employed by the organism to protect itself against the invasion of the parasites. When the biliary ducts become infested with the coccidium oviforme, the first phenomenon observed is an intense congestion of the vessels, accompanied by an emigration of leucocytes.¹ After a time, larger mononucleated amoeboid cells appear. The exact origin of these is still a matter of discussion, so much so that one observer has pledged himself in turn to two diametrically opposed opinions. However this may be, these cells, derived either from the wandering or mesoblastic cells, develop into delicate connective tissue, and later on into fibrous tissue, which, penetrating between the proliferating epithelial cells, ultimately forms a complete envelope to the small tumour. We have then a typical parasitic adenoma, the stroma of the tumour protecting the organism against the invading parasite. Before and during the time that this capsule is being formed, one may not infrequently see amoeboid cells penetrating between or into the epithelial cells even, and eating up naked and occasionally even encapsuled protozoa.

When the tumour is formed, the process of defence is not arrested. Large mononucleated and multinucleated amoeboid cells gradually form a wall around the contents of the little tumour. These cells send out long prolongations, surround the protozoa, and take them into their interior, where they obviously undergo a process of encapsulation, or are ultimately digested. At the same time, however, the fibrous tissue forming the stroma of the tumour becomes denser, and gradually the entire tumour is converted into a small mass of fibrous tissue. The disease might then be considered as cured, locally at least, were it not for the fact that one may still find in such nodules typical coccidia, which, however, are completely surrounded by a giant cell; and it has been shown that the coccidia, when encapsuled, possess considerable powers of resistance to chemical and other reagents.

Another example of an identical process is that which is seen in the coccidial tumours which infest the intestines of sheep. Here also may be observed the formation of a dense capsule of fibroid tissue derived from the granulation tissue surrounding and isolating the proliferating epithelial cells containing the parasitic protozoa, and which sends out offshoots which form the stroma of the tumour. There is this difference, however, that the connective tissue never completely surrounds the tumour, so that the epithelial cells are free to proliferate towards the lumen of the alimentary canal. The result is that the tumour gradually becomes elongated at its base, and finally hangs by a kind of pedicle in the lumen of the tube. These appearances give us cause for belief that many polypi—even non-malignant polypi—

I may remark that our later researches have not altered my opinion, and that I still hold, and am more and more convinced, that scar tissue is, in the major part of cases, if not always, derived from emigrated cells. I confess, however, that up to the present moment the crucial experiment which is to settle this question has not yet been discovered.

which grow in open cavities of man and animals, may perhaps have a similar parasitic origin.

We now come to what is perhaps one of the difficult points, namely, the way in which the human organism resists cancer.² Examine the periphery of an actively growing tumour, of the breast for instance, and you may occasionally find that the cancer cell is not separated from the surrounding fat by any layer of lymphocytes or connective tissue whatever. Cut a section of an actively-growing metastasis of the same cancer in the liver, and you may find that the cancer elements are in close contact with the liver cells, but that the latter are flattened and evidently degenerated. It might be disputed whether this flattening and degeneration are produced by pressure, or by a process of digestion due to some poison secreted by the cancer cell or its parasite, but we may waive this point. In the majority of instances, however, there is a distinct collection of lymphocytes, and in abdominal cancers and actively growing metastases, one may often see that these small round cells penetrate into the interior of the epithelial cell and of the parasite, or else surround the latter and destroy it. In many tumours, however, especially in primary tumours of the breast, such a phenomenon is but rare, and I will now show you that in the majority of cases the means of resistance consist in the connective and fibrous tissues forming the stroma of the tumour.

As we proceed towards the central part of the growth these lymphocytes become converted into larger mononucleated cells, and later on into connective and fibrous tissue, which surround and imprison these cancer cells. At the same time, some of these cancer cells degenerate, and this degeneration is due to a true process of digestion on the part of the connective tissue—for example, the stroma of the tumour, and not simply to pressure, as is maintained by most. The stroma, when it hardens into fibrous tissue, is simply scar tissue, and few will deny that the function of the scar which covers a wound is to protect the organism against noxious agents coming from without. Similarly, in cancer the connective tissue serves a useful purpose in protecting the organism against the invasion of cancer.

One might think that these mesoblastic cells had no power of discriminating between cancer cells and parasites, or even between living and dead cancer cells. It is, however, a peculiar fact that in some cancers the epithelial cells degenerate with an amazing rapidity, and that in such tumours large tracts are found which contain nothing but these degenerated cells and no parasites. Now, the mesoblastic cells have no liking for such degenerated patches, so that one may have to look through several fields before a single leucocyte can be seen. Even the fibrous tissue does not as a rule penetrate into the degenerated tracts, but simply forms a capsule around instead of pushing its processes into the interstices between the dead cells, as it does between the living ones. This condition, therefore, is similar to that found in actinomycosis, in which disease the islets of dead cells and parasites remain untouched by wandering cells, though a dense capsule of connective tissue forms around. You see, therefore, that it is not without reason that some competent observers have described cancer as a granuloma, for in it we really find all the lesions of a parasitic granuloma, plus another lesion, namely, the proliferation of epithelial cells. The infiltration of round cells at the periphery corresponds, for instance, to the young tuberculous nodule, and the stroma in the interior to the fibrous part of an old tubercle. I do not propose to enter into the question as to whether this proliferation of epithelial cells may not be in itself a protective process, though many and weighty arguments could be brought forward in its favour, for the developing of such an argument would carry us too far. But I would sum up this part of my lecture by saying that in malaria, the psorospermiosis of the rabbit, and in cancer the process which enables the organism to resist is practically the same; for the destruction of the hæmatophyllum malarie by a leucocyte, or the encapsulation of a cancer cell and its contained parasite by fibrous tissue, are identical processes, differing only in the time which they occupy. The stroma of a malignant tumour—

² I may remark that in sarcoma, it is not uncommon to find large macrophages crammed with cells in a more or less advanced state of intracellular digestion.

may, therefore, be described as the safeguard of the organism.

An attempt has been made to show you the characteristics common to all these diseases, but the lesions which apparently make of cancer a disease *sui generis* must at least be briefly indicated. In cancer the epithelium cells not only proliferate in the neighbourhood of the infecting protozoa, but the cells change their character to some extent, and invade the neighbouring tissue. A cell from a cancer of the breast, for instance, is in shape and size unlike its parent cell normally found in that organ, and, moreover, it may find its way into any part of the body. These are the most striking differences which we have now to examine, but are they of fundamental importance? We think not. And if we once grant that protozoa may cause a proliferation of epithelium cells—an hypothesis which, in view of what we have just stated concerning the coccidium of rabbits and sheep, may not be unfairly admitted—it is possible to account for all the other lesions mentioned.

We have seen that the epithelium cell holding in its interior the peculiar protozoa of vaccinia undergoes certain changes which resemble those found in cancer. The nucleus of the cell becomes more apparent, and often irregular, the protoplasm more oedematous and larger, the whole assuming a more rounded form. True, it does not show a marked tendency to invade the deeper tissues, but may not that be simply due to the fact that the inflammation which accompanies this infection and the acute character of the illness do not give it a chance to do so? In the coccidial tumours of the rabbit, and of the sheep, we have seen that the proliferation takes place in the direction of least resistance, and that its extension is prevented by the formation of fibrous tissue. In cancer an attempt at encapsulation is also made, but is never entirely successful. We have here the same difference in the reaction of the organism as exists between a local disease and a general infection due to bacteria.

This difference between the cancer cells and the normal epithelium cells is only a question of size. It is not a physiological one, nor even a really morphological one. As has long ago been pointed out, the cancer cells coming from the skin, for instance, have in the main the characteristics of epidermic epithelium cells, and in fact, as the founder of cellular pathology has ably put it, "No kind of cell tissue which can occur in our body is in the strict sense of the word atypical."

The objection that the cancer cell invades the surrounding tissue, whereas this never happens in any other form of disease, may, without too much ingenuity, be met by the supposition that the pressure of the proliferating cells or the secretion of the protozoa weakens the resistance of the surrounding tissues. Indeed, there is very distinct evidence of this in the metastases which grow in glandular organs—in the liver, for instance, in which even cells situated some distance from the tumour, where there is no evidence of pressure, undergo fatty degeneration and other changes. The formation of the stroma is easily explained by the irritation produced by the protozoa, and we may not unreasonably suppose that the parasites secrete poisons which, like those secreted by micro-organisms, attract amoeboid cells; and that the differences in the amount of reaction may be due to the possibly differing strengths of the poisons, or to the age, sex, and other influences which affect the resistance, if not to the fact that the parasite has to act through a screen, as it were, instead of acting directly. The presence of the stroma in cancer, the emigration of leucocytes into epithelium cells, and the other inflammatory reactions accompanying the presence and growth of a cancer, are, in our opinion, the strongest evidence that it is a growth of parasitic origin.

The fact that the metastatic growths resemble the parent one, and not the tissues in which they become implanted, must be shortly discussed. A metastatic cancer of the rectum, for instance, implanted in the liver produces another cancer resembling the primary tumour. Again, we believe that if it be admitted that the protozoa of cancer produce proliferation of epithelium cells this fact may be readily explained.

In the first place, let us examine the proposition a little more closely, and to show the fallacy contained in it let us take for our text the very words given in the most popular

textbook now used by students. After describing the formation of a secondary nodule in the liver, the author sums up his description by saying: "a secondary nodule is at length evolved *whose structure resembles in all points the structure of the parent nodule.*"

This statement as it stands is inaccurate, for it says too much. I should, however, have no objection to it if the words "the epithelium cells of which resemble in all points those" were substituted for the words placed in italics. For what does the author mean by the structure of the parent tumour? Does he mean that part of the parent tumour which is one week, or that which is three years old? The point is of importance, for were he to compare the young metastasis with the older parts of the parent tumour, or were he to place side by side a section of the growing edge of the parent tumour and an old metastasis, the epithelium cells would, no doubt, resemble each other in all four specimens; but that would be the only resemblance, for the amount and structure of the stroma of the metastasis depend as in the primary tumour on the age of the metastasis, and on the resistance of the individual towards cancer.

The epithelium cells in the metastases must resemble the parent cells in their structure as in their arrangement and physiological properties, for experiment has shown that even normal tissues, when successfully transplanted, not only reproduce themselves for a time, at least, in the same way, but possess the same arrangement and physiological properties as before. It would therefore be astonishing, indeed, did the cancer cells not reproduce themselves in the metastases in exactly the same manner as in the parent tumours. And remember that the cancer cells which form the metastasis contain the parasitic protozoa, which may again give rise to proliferation of cells. We can then easily account for the stroma, and also for all the other anatomical appearances of cancer, provided we can prove that protozoa of cancer will produce epithelial proliferation. Have we any evidence to show that the protozoa present in cancer cause multiplication of cells? I have shown you that in certain diseases the protozoa cause epithelium cells to proliferate, but that in many other they do not. We have, therefore, no right to say that those of cancer must necessarily do so, for the simple reason that no one has ever experimentally produced proliferation of the epithelium cells by the experimental inoculation of a pure culture of cancer protozoa; but, on the other hand, there is nothing to prove that these protozoa may not have that action, and there is strong probability that they do. We have, in fact, arrived at a standstill, and at a point where one might just as easily argue that the parasitic protozoa of cancer infest the epithelium cells because these proliferate, as that the cells proliferate because of the presence of protozoa. We think that, as far as the physiological action of these protozoa are concerned, we have learnt as much as can be learnt from anatomical observations, and that the time has now arrived for experimentation on animals.

In conclusion, let me hope that I have not appeared to you to have spoken in somewhat too confident and dogmatic a tone. I am aware also that many of the facts which I have brought forward to-night are controverted or differently explained by pathologists of reputation and sterling merit. The knowledge that what I have said has been said before a skilled audience, and will, when published, be sharply criticised, has emboldened me to speak freely, for the fair criticism of others is a good and wholesome discipline, for which every man ought to be thankful, and I should be the last to complain of hard hitting. My object has been to show that the hypothesis that cancer is of parasitic origin is worthy of all consideration, and that the differences between cancer and other diseases undoubtedly caused by protozoa are not so great as they at first sight appear to be. Let our ambition now be as Hunter's was: "The experimental analysis of life in health and disease."

DR. LOUIS JULES FAUVELLE has bequeathed to the Paris Anthropological Society a sum, the interest of which, amounting to 2,000 francs (£80), is to be offered as a prize for the best monograph dealing with the structure of the nervous system or with nervous influence.