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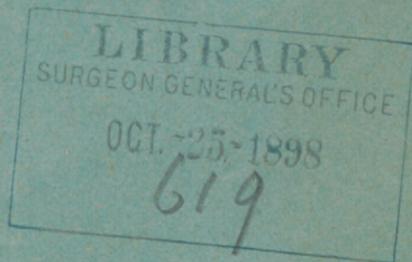
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Protozoa and Carcinoma.

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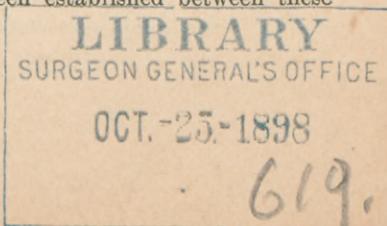
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ANYONE surveying the literature that has accumulated during the last few years on protozoa and their relations to malignant tumors and especially to carcinoma, will no doubt be struck by the apparently hopeless tangle of contradictory observations and theories. A closer scrutiny, however, discloses certain fundamental lines along which all this mass of research and speculation can be arranged.

For the last three years I have been steadily engaged in a study of cancer with regard to the question of protozoic parasitism and certain other points of its histology. More than sixty carcinomata from various regions of the body have been examined, besides numerous sarcomata and non-malignant growths. The pieces of tumor were in every case taken immediately after removal, and in many instances small pieces of tumor were removed before the operation in order to insure fixation of the tissues in a state approximating as closely as possible to that of actual life. Pieces of each tumor were invariably dropped at once into various fixing solutions, one of these in the last year being always a concentrated bichloride of mercury solution according to Heidenhain or Hanseemann. They were then in the usual manner hardened, imbedded in paraffin or celloidin, cut with a microtome into thin sections varying from 1 to 10 μ , and stained according to numerous methods. Thus thousands of sections were examined and compared. I desire to express here my grateful obligation to Drs. Willy Meyer, Kammerer, Krug, Gerster, and F. Lange, to whose kindness I am indebted for the greater part of this valuable material. I trust to be enabled at not too distant a date to submit some slight contributions to our knowledge of the more minute histology and pathology of cancer. In the following lines I propose to briefly sketch the present status of the question concerning the relations of protozoa to carcinoma on the basis of a careful consideration of the publications of others and of my own work.

The two fundamental questions that claim our attention are:

1. Has the presence of parasitic protozoa in carcinoma been demonstrated beyond possibility of doubt? and
2. If so, has any etiological relation been established between these parasites and the neoplasm?



The existence of certain pathogenic protozoa is now a sufficiently well established fact. The *plasmodium* (*hæmatophyllum*) *malariae*, the *amœba* of dysentery and certain other forms of enteritis, the *coccidium oviforme* of the rabbit, are well-known instances. All these are, however, easy of recognition. The *amœbæ* can be traced in the dejections whilst still alive, and by their movements and peculiar structure are not readily confounded with any other cells. Once observed during life they can without much difficulty be recognized in the stained and hardened tissues.

Again, *amœbæ* are not intra-cellular parasites, and *coccidium* has so well-marked a cycle of development, and is in the encysted state so conspicuous and characteristic an object, that a mistake in diagnosis is hardly possible. In the *hæmatophyllum malariae* we have indeed an intra-cellular parasite, and for some years the controversy was maintained with much earnestness whether or not it was a true parasitic organism or some form of degeneration of the erythrocyte. The parasites can, however, readily be observed while living and moving within the red blood-corpuscles. There is, moreover, in a certain sense a specific stain, inasmuch as methylene-blue does not stain the blood corpuscles while it does stain the plasmodium. A tolerably well marked developmental cycle has also been demonstrated, thus leaving no possibility of doubt of the protozoan and parasitic character of the plasmodium.

But on what indisputable basis can we establish the diagnosis of protozoan parasites in cancer? We have to deal here with conditions the complexity of which is only just beginning to be recognized. The observation of the living tissues is encompassed by almost insurmountable difficulties, and we are compelled to depend almost exclusively on a study of artificially fixed, hardened, and stained specimens. A comparison of sections of different pieces of the same tumor fixed respectively in Flemming's solution, picric acid, alcohol, and bichloride of mercury will readily demonstrate the widely different appearances resulting from different methods of fixing and hardening. Noeggerath,⁴⁸* Gibbes,²⁸ and others have already pointed out this source of error, and I would again urge that only such results are comparable as have been obtained by precisely the same methods of preparation.

Besides the artefactions due to the processes of preparation, the cell metamorphoses must also be taken into account. The more closely the subject is studied the more the conviction is forced upon the observer that numerous alterations, regressive as well as progressive, are continually going on in cancerous tissues. A wide field for research is open here, and its investigation has as yet not passed beyond the very first stages. Degenerations of all kinds (hyaline, colloid, gelatinous, horny,

* The numbers refer to the table of references appended to this paper.

etc.), vacuolization and dropsy of the cell bodies, irregularities in the distribution of the chromatin, dispersion of chromosomes and fragments of such during and after the karyokinetic process, asymmetric mitosis, cell invaginations, intra- and inter-cellular invasion of red blood-corpuscles and leucocytes, either normal or variously degenerated—all these and numerous other irregularities must be most carefully studied in this connection.

We must take into consideration also that no specific stain for protozoa has as yet been discovered. It can readily be shown that cells manifestly degenerated, whose derivation from healthy cells is made apparent by a full line of intermediate stages, will stain differently from healthy cells with many, or all, of the usual aniline or hæmatoxylin dyes. Metachromatism, therefore, can by no means be depended on in every case as a safeguard against error.

The bacteriological methods, so marvellously successful with bacterial microbes, have thus far entirely failed in the case of protozoa. In spite of numerous and determined efforts no method of culture has as yet led to any practical results.

How, then, can we arrive at the diagnosis of a protozoan parasite in cancer? The difficulties seem almost insurmountable. No methods of pure culture, no specific stain, hardly a possibility of examining living tissue, and a multitude of cell metamorphoses in the tumor which tend to simulate parasitic cell-enclosure.

According to the present very imperfect knowledge of everything connected with this subject the answer to the question can, in my opinion, be only this:

We are justified in making a diagnosis of a protozoan parasite in cancer only when its morphological attributes and its reaction toward stains are such as to preclude all possibility of being explained by any of the numerous kinds of cell metamorphosis or other irregularities of cell life hinted at above, and when, in addition thereto, a sufficiently well marked and well established developmental cycle can be demonstrated.

If now the work done within the last few years on protozoa in carcinoma be tested by this standard, it becomes apparent that by far the larger part of what authors have claimed as parasites cannot unconditionally be accepted as such. It will be readily comprehended, too, why so little uniformity of results has been obtained. While some observers find the principal seat of the parasite within the nucleus, others deny the existence of intra-nuclear bodies altogether and locate the protozoön principally in the protoplasmatic cell body or between the cells. A glance at the illustrations furnished by Wickham,⁵² Steinhaus,⁷¹ Foà,⁵⁵ Podwyssozki and Sawtschenko,⁵⁶ Soudakewitsch,⁷⁰ Sjöbring,⁶⁹ Pfeiffer,⁵⁴ and others will demonstrate what widely differing objects were claimed as parasites, though it cannot be denied that certain typical forms reap-

pear in the work of nearly all of these authors. While certain authors—Albarran,² Malassez,⁴¹ Darier,¹⁷ Wickham,⁸² Ramsay Wright,⁸⁴ Russell,⁶³ etc.—are convinced of the abundant and constant occurrence of protozoa in carcinoma, others, among whom may be mentioned Borrel,⁴ Firket,²⁴ Klebs,³⁵ Ribbert,⁵⁸ Shattock and Ballance,⁶⁷ are inclined to deny their existence altogether, and explain the histological appearances which have been classed as protozoa, as due to some of the numerous cell irregularities which are known to occur in cancer. Particularly Török,⁷⁸ in a very careful study of the subject, has recently pointed out where some of the prominent adherents of the parasitic theory have, in his judgment, been at fault. Still other investigators, such as Steinhaus,⁷¹ Podwysoski,⁵⁵ Stroebe,⁷⁴ Siegenbeck van Heukelom,⁶⁸ reserve their judgment, and while admitting that much that has been regarded as parasitic is due to some form of cell metamorphosis, still contend that certain cell-enclosures which they picture can best be explained on the supposition that they are stages in the development of a protozoan parasite.

As regards my own work on the subject and its results, I hope on a subsequent occasion to give a more detailed account. I wish here to state very briefly that in all the very large mass of material examined, nothing has been observed but what could easily be explained without having recourse to the assumption of protozoan parasites. The majority of the appearances described and portrayed by other investigators were recognized, but in no case could I convince myself of the protozoan character of the objects, according to the principle enunciated above. On the whole I can subscribe to the views expressed by Török.⁷⁸

Within the last few weeks Korotneff's investigations⁴⁰ have appeared. He describes a new parasite, *Rhopalocephalus carcinomatosus*, with all its stages of development, and regards it as specific in cancer. I have as yet not had time to follow his methods and attempt a verification of his statements. The material on which he bases his observations is extremely limited. Nevertheless if competent observers will substantiate his results, it seems probable that here we have a true parasitic protozoön in cancer, fulfilling all the conditions required by our fundamental principle (*cf.* Korotneff's Figs. 1, 2, 15, 19, 21, 46, etc.).

Somewhat similar observations, though attained by different methods, have also been published by Sawtschenko,⁶⁴ and I am inclined to think that here also we have to deal with a true parasite. The observations of Burchardt⁸ may possibly also come under this head.

As a result of the entire discussion it seems safe to say that while the large mass of cell-enclosures and intra-cellular bodies prematurely regarded as protozoa have no claim to this title, it seems highly probable that protozoan parasites can and do occasionally occur in carcinoma.

What relation have protozoa to carcinoma? Is there an etiological

connection, and are we justified in the present state of our knowledge in assuming a parasitic origin of cancer?

At this point of the inquiry it becomes important to consider if the investigation of protozoic parasites throughout the animal kingdom has thus far brought to light any tumors due to parasitic action that can be classed as true cancer, or at least as analogous to it.

It would seem that the animalcules in question are in some instances perfectly harmless cell-parasites. It is true, the host-cell is usually destroyed, but there is no injury to the surrounding tissue nor to the organism as a whole. As examples of this may be cited the *Klossia helicina* in the snail-kidney, and the *monocystis* forms in the testicle of lumbricus. In other cases the presence of the parasite causes mechanical and chemical irritation. We must suppose that the *plasmodium malaricæ* destroys its host-cells, and, tainting the blood with the products of its metabolism, produces the characteristic symptoms of malarial fever.

As an instance of the extra-cellular parasite, the amœbæ of dysentery presumably produce their characteristic symptoms by chemical irritation as a consequence of their peculiar metabolism.

There are, however, certain forms of protozoa which cause distinct proliferation of the surrounding tissue and thus produce well-marked tumors. To Pfeiffer we are indebted for the knowledge of such tumors caused by *micro-* and *myxo-sporidia*; and the tumors caused by the various forms of *coccidia*, particularly by the *coccidium oviforme* of the rabbit, are brought forward again and again as a convincing argument by the unconditional adherents of the parasitic theory of cancer.

Delépine and Cooper²² have very recently shown that the *psorosperm-osis* or *gregarinosis* of the rabbit in very numerous instances causes no morbid symptoms whatsoever, and interferes neither with the life nor the health of the animal, though after death numerous characteristic fibrous nodules can be found disseminated through the liver and intestines. Sometimes, however, and owing to conditions as yet obscure, the coccidial invasion causes morbid symptoms, and among others tumor-like nodules, particularly in the liver. Such tumor-nodules I have carefully examined. I find in accord with most authors on the subject, besides considerable new-formation of connective tissue, infiltration of leucocytes and broken-down cell material, a slight but distinct though not always constant proliferation of epithelium, principally of the bile-ducts.

Of tumors caused by *micro-* and *myxo-sporidia* I have no experience, but conclude from the descriptions given by Pfeiffer that they do not materially differ in any fundamental point from those caused by *coccidia*.

Are we justified in considering such tumors as analogous to cancer? It is well to call to mind here that cancers should not be considered as a

mere proliferation of epithelial cells. If such proliferation were to be considered the distinctive feature, then every acuminate condyloma, every papilloma, every adenoma would have to be classed as carcinoma—tumors in which the epithelial proliferation far surpasses in magnitude anything produced by the comparatively insignificant proliferation due to protozoa. It is necessary continually to keep in mind that the distinctive characteristics of cancer are, not the mere fact of the proliferation of epithelium, but the new-formation of epithelium and stroma* in a typical manner; the power to produce metastatic tumors in distant parts of the body which faithfully and under all circumstances reproduce the structure of the primary tumor, entirely independent of the character of the tissues in which the secondary nodules are seated; and, thirdly, the general cachexia which, according to the investigations of Klemperer³⁶ and of Müller,⁴⁶ may possibly be due to toxic products resulting from the morbid metabolism of the cancerous tissues. With this view of cancer before us we must come to the conclusion that the tumors thus far recognized as undoubtedly due to protozoic influence have nothing in common with true carcinoma, are in no way analogous to it, but present all the characteristics of chronic irritation or inflammation.

Experiment and observation have abundantly proved that ordinary epithelium when floated by the blood or lymph current into a locality foreign to its nature, though it may remain alive for a while, will certainly not proliferate to any extent, and finally will be infallibly destroyed. Not so with cancerous epithelium. We must accept it as a fact to-day that metastatic cancers originate from particles of the primary tumor bodily transported to distant localities where they proliferate and reproduce the structure of the primary growth entirely independent of the histological character of the encompassing tissues. It seems difficult to grasp how the chronic irritation or the toxic influence of a parasite can produce, for instance, a rectal cancer. We see here tubule after tubule with cylindrical epithelium cells, basement membrane, typical arrangement of the stroma, and all, though in a state of wild proliferation, still simulating the normal structure. But how can parasitic action explain the fact that a few particles of this rectal tumor, when transported into the lung or the liver, will produce, not a formless jumble of epithelial cells, but the exact fac-simile of the primary tumor—tubules, stroma, and all the other characteristics? We must agree with Councilman¹⁶

* I desire to mention incidentally here that it seems probable that the old theory of Thiersch and Boll, according to which the stroma plays a merely passive part in the histogenesis of carcinoma, and the proliferation of epithelium is due, in a great measure, to the disturbance of the vital equilibrium supposed to exist between epithelium and connective tissue, in favor of the former, will need reconsideration. There are good reasons for believing that very active and quite characteristic processes that have their origin in the stroma can be shown to play an important part in the pathology of cancer.

that we have here, according to our present lights, an insurmountable barrier to the theory of a parasitic origin of cancer.

Another problem, as it seems to me, entirely inexplicable by the parasitic theory is presented by certain observations comparatively rare, but sufficiently well attested and studied. I refer to those cases of congenital carcinoma in which both parents are free from tumor and remain healthy.

But leaving theoretical considerations aside, do the actually ascertained facts warrant us in assuming a parasitic origin of cancer? According to the principles long ago laid down by Koch, the following would be necessary in order to establish an indubitable etiological connection between parasites and carcinoma: We would have to find a specific and well-marked micro-organism constantly occurring in every case of carcinoma and in such distribution and topographical arrangement as would suffice to explain the anatomical facts. Pure cultures of this micro-organism would have to be obtained outside of the body; and lastly, methods would have to be found by which inoculations with these pure cultures would reproduce typical cancer.

All attempts at obtaining cultures of protozoa from cancer have thus far entirely failed. The innumerable experiments with a view to a reproduction of cancer by inoculation and transplantation have led to no results. The successful transplantations of Hanau, Wehr, Hahn, and Von Bergmann, though most important, cannot be utilized in this connection.

There remains, then, only the question of the occurrence of specific organisms and their characteristic distribution. I have endeavored to show above that no such specific protozoa have as yet been demonstrated, and that, while it is probable that several kinds of protozoa do occur, they are by no means to be found in every cancer nor in any characteristic distribution. In fact the very earliest metastatic invasion of lymphatic glands, where only very few epithelial cells are as yet distributed through the lymphatic tissue, and where, if at all, one would expect a most unmistakable and vigorous crop of parasites, I have invariably found free from anything resembling protozoa. Ruffer, indeed, finds his cancer-bodies not only of constant occurrence in every form of cancer, but also in characteristic distribution, and lays particular stress on their constant presence at points of most rapid growth. According to our standard laid down above, however, the protozoan nature of these cancer-bodies has by no means as yet been established, and the objections of Vitalis Müller⁴⁷ and others are not disproved. Further investigations will have to clear up these doubts, particularly as some recent very interesting experiments of Power⁵⁷ seem, after all, to point toward a possibly specific character of these bodies.

It is well to note *en passant* that in sarcoma, so totally different from

cancer in structure, cell-enclosures hailed as possible parasites have also been described. (Steinhaus,⁷⁸ Pawlowsky.⁵⁰)

Recognizing in a measure the insufficiency of the cell-enclosures heretofore described as a basis for a parasitic origin of cancer, two works have recently appeared in which a different view of parasitism is taken.

Adamkiewicz¹ boldly asserts that the cancer cells are not epithelial in character, nor derivatives of epithelial cells, but themselves the full-grown parasites, and the small-cell infiltration so well known in the histology of cancer, their youthful stage (zoöspores). These parasites produce a toxin closely related to neurin, which, when properly administered, has a decided curative effect upon cancerous disease. It is needless to criticise this book here. Schimmelbusch, Hansemann, Paltauf, have said all that need be said on the subject. I will only mention that the crucial experiment on which Adamkiewicz bases his entire theory, the effects, histological and pathological, of implantation of small pieces of cancerous tissue into a rabbit's brain, has been carefully repeated by Geissler, who has conclusively shown that Adamkiewicz's results are based upon errors due to incomplete asepsis.

The other work is by L. Pfeiffer,⁵⁴ to whom we are indebted for so much of our knowledge concerning pathogenic protozoa. After a careful survey of protozoic parasitism in the lower animals and various forms of human disease, he treats of cancer as of undoubted parasitic origin, classifying the protozoön in question as *amæbosporidia*. He studies cancer principally in metastatic nodules in muscular tissue, and accepting the cell-enclosures described by Wickham* and others as representing certain forms in the development of his parasite (*dauerform*), he seeks to establish a complete and characteristic developmental cycle.

While paying tribute to the erudition and indefatigable labor and enthusiasm of the author, it must nevertheless be confessed that his arguments are far from convincing. He, too, assents that at certain stages of their development the parasites cannot be distinguished from the ordinary epithelial cells. At another stage they resemble leucocytes so closely that the usual small-cell infiltration of cancer is unhesitatingly identified with the spores of parasites. The cardinal facts in the histology and histogenesis of carcinoma are in a great measure ignored in the speculative enthusiasm of the new theory. The beautiful photographs with which the book is profusely illustrated are entirely inadequate as convincing proofs of the author's opinions.

* Power's experiments on the effect of chronic irritation on the epithelium of the rabbit have again proved that much of what numerous investigators, and especially Wickham, have described as protozoa (*psorosperms*) is nothing more than cell degeneration. Of Paget's disease I have no personal experience, but through the kindness of Dr. Lustgarten I have had the good fortune to examine fresh material from a case of Darier's disease (*psorospermose folliculaire végétante*). I can only verify the statements of Boeck and of Petersen that there is no proof of the existence of the protozoön, and the so-called psorosperms are in all probability degenerated cell-enclosures and cell-invasions.

In concluding this short review we would sum up as follows :

The existence of parasitic protozoa in cancer is probable, though the greater part of what has hitherto been described as parasitic is certainly not so. No constant or in any way specific organism has as yet been demonstrated beyond possibilities of doubt. At present no facts, histological or otherwise, compel the assumption of a parasitic origin of carcinoma, while there are very strong and valid arguments against such assumption.

For many years to come the indefatigable efforts of numerous investigators will be required to throw light on this most obscure of diseases. A more intimate penetration into the mysteries of cell structure and cell life, both in health and in disease; a closer study of the living tumor tissues; an endeavor to clear up the, as yet, entirely obscure chemistry of neoplasms—on these lines, no doubt, advances in our knowledge will be made. Nor should the further study of protozoa be neglected, but it should always be allied with coolest criticism and never leave the *terra firma* of experiment and fact for the airy region of wild theorizing and speculation.

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