REMARKS ON CARCINOMATA AND COCCIDIA.¹

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In a review published quite recently, M. Baumgarten² reproaches M. Ziegler, the author of the treatise on pathological anatomy most widely read at present, with not accepting Cohnheim's theory respecting tumours. In M. Baumgarten's view this theory "is for the present the only acceptable, and probably also the only true one, of all the theories put forward in this most obscure branch of pathological histology."

Cohnheim's theory of tumours, which is widely accepted by pathologists, especially in Germany, is that tumours in general, and malignant tumours in particular, are due to the exaggerated vegetation of primary foci detached from the embryonic folds, and gone astray in different parts of the organism. These stray germs of tumours may (according to Cohnheim's theory) exist during a series of years, or of decades, without giving any sign of their presence; but after a long period of inactivity the particles of the embryonic fold begin to proliferate in an extraordinary manner, over-running the individual, and in the end killing him.

This theory is not deduced from facts established by scientific methods, but has been built up in a purely speculative manner, and rests only on probabilities. As embryonic folds are peculiar to all metazoa (that is to say, multicellular animals), it is quite natural to suppose that invertebrates are also suitable subjects for the development of tumours analogous to those of man and the superior animals.

Monstrosities due to the abnormal development of different parts of their organism are often observed in all kinds of vertebrates; but although the inferior animals possess an ectoderm and an endoderm like vertebrates, nothing has ever been found in them resembling epithelial tumours.

Amongst the very numerous diseases of the inferior animals (insects, crustacea, worms, etc.) many infections are found, but never cancer. If, however, for the production of this latter, only a fragment of a stray embryonic fold is required, it is not clear why invertebrates should be exempt from such growths. On the other hand, invertebrates, and inferior organisms in general, present numerous cases of tumours, only these tumours are always of parasitic origin. Everyone is familiar with the galls which vary so much in many plants; these are veritable tumours, developed in consequence of abnormal proliferation of the vegetable cells; but the cause of these neoplasms is always found to be a parasite which has found its way into the plant.

Amongst invertebrates also tumours have been observed. Polypi present abundant vegetations around the foreign animals which have penetrated into the mass of the polyparies. The same rule is therefore always confirmed. In the lowest scale of living things all neoplasms are of parasitic origin. There are infectious tumours, but there are none of the fragments of embryonic folds detached and transformed into neoplasm.

Is it not possible that man and the superior animals may be subject to the same law, and that in them also true neoplasms, and especially malignant tumours, may have a parasitic origin? This supposition, raised many times in pathology, has generally been rejected by the medical profession. This is how Cohnheim, the author of the embryonic theory of neoplasms, formulates his criticism of the parasitic theory:—"Never," he says, "has any epidemic or endemic of true tumours been observed. Further, it has never been possible to prove the transmission of a tumour from one individual to another. Never has a surgeon infected himself with a tumour during an operation, neither has a man ever been known to

have contracted cancer of the penis in consequence of his wife suffering from uterine cancer. And how many fruitless experiments have been made with the object of transmitting tumours from man to animals, or from one individual of the same species to another." During the ten years which have elapsed since the publication of these lines, our ideas as to infection have been greatly modified. Nobody would be surprised to know that a disease which had spread all over the earth had turned out to be an infectious disease of parasitic origin. Tuberculosis has nothing of an epidemic or endemic character; but, in spite of that, it is really due to the parasitism of Koch's bacillus. The absence of contagion insisted on by Cohnheim cannot be adduced as negating the parasitic nature of a disease. Miasmatic diseases, though not contagious, are none the less infections due to microbic parasitism.

In Cohnheim's day the history of the coccidian disease of rabbits, which is interesting from several points of view, was already known. It will not be a useless digression if, before approaching the principal subject of this paper, we dwell for a moment on this "coccidiosis," the knowledge of which throws much light on the question of cancer.

1. In the liver of the rabbit are often found greyish or white nodules, composed of a thick membrane, enclosing caseous or puriform contents. On examining with the microscope the products contained in these "tubercles," we find in them a large number of "coccidia," or oval bodies closely resembling the ova of entozoa. In young rabbits the presence of these organisms engenders a disease which often proves fatal, whilst full-grown rabbits tolerate parasitism without suffering any great harm.

Fig. 1.—Coccidia of rabbit.

The coccidiosis of rabbits is, therefore, certainly an infectious parasitic disease. Nevertheless, it is never transmitted by true contagion. If nodules of liver containing masses of coccidia are given to a healthy rabbit to eat, the disease will never be engendered. The coccidia which are swallowed will be digested, and infection will not take place.

Coccidiosis, not being a contagious disease, is accompanied by true tumours. If sections of the nodules of liver are examined, it is easily seen that they are formed by abundant vegetations of the biliary ducts, surrounded by a more or less thick layer of connective tissue. The epithelium of the ducts retains its ordinary properties, and is only distinguished by a considerable hyperplasia, giving rise to the formation of numerous ramifications.

Fig. 2.—Hyperplasia of the biliary ducts of the rabbit under the influence of coccidia.

Here, then, is an example of a malignant and non-contagious tumour. Shall we, then, say with Cohnheim that it is not infectious? No; because the parasite which causes the tumour is a voluminous organism the existence of which, and the part played by it, can no longer be doubted.

The coccidiosis of rabbits is a miasmatic infection. In order

[1667]

¹ The illustrations have been kindly supplied to us by the Editor of the *Revue Générale des Sciences Pures et Appliquées*, in which the article originally appeared.

² *Berliner klinische Wochenschrift*, 1892, p. 730.

³ *Allgemeine Pathologie*, 2nd edition, 1882, p. 735.

that they may give the disease to fresh rabbits the oval coccidia must first undergo a definite transformation, which only takes place outside the organism. In sand, in earth, or in water, in suitable conditions of temperature (15° to 25° C.) and of aëration, the contents of the coccidia divides into four cells, and is transformed into four spores, provided with a very resistant external covering. Each spore encloses two falciform and very delicate embryos which give birth to new parasites, and thus engender the terrible disease when swallowed in polluted food; the sporiferous coccidia penetrate into the digestive canal of rabbits. The envelope of the spore protects the falciform embryos against the action of the gastric juice, and allows them to pass into the intestines and into the liver. The epithelial cells of the small intestine and of the biliary ducts become the seat of infection. The young coccidia, under the form of small round bodies, insinuate themselves into the protoplasm of the epithelial cells, where they grow and become transformed into oval parasites representing the adult form.

Fig. 3.—Coccidium enclosing four spores.

Fig. 4.—Epithelial cell of rabbit with a young coccidium.

But side by side with this cycle of development there exists another, discovered by M. R. Pfeiffer,⁴ of Berlin. The round bodies divide into a large number of segments, which become transformed into a stage of growth, the meaning of which has not yet been determined. It is probable that these forms in growing propagate the infection in the organism of the rabbit attacked with coccidiosis. They serve also to increase auto-infection, whilst the spores (developed outside the organism of the rabbit) act the part of a true miasma.

In the coccidiosis of the rabbit we have, therefore, an example of an infectious miasmatic disease, produced by coccidia, the presence of which in the organism of the rabbit induces the development of a true malignant tumour.

Let us see what use this disease of rodents presents in regard to human pathology.

2. Are there coccidian diseases in man? This question has been decided in the most positive manner, thanks to M. Laveran's discovery of the parasite of malaria. The microbe of this disease is an intracellular parasite, like the coccidium of the rabbit, but whilst this latter vegetates in the protoplasm of the epithelial cells of the biliary ducts and of the intestines, the microbe of malaria penetrates into the interior of the red corpuscles of the blood, where it finds the necessary conditions for the support of its life.

The parasite of malaria has this in common with the coccidium of the rabbit that it shows itself in the form of a small spherical body, and forms crescents. (Fig. 6, b, c.) But

Fig. 5.—Crescent-like bodies of rabbit's coccidium.

beyond this it has an amœboid stage (Fig. 6, a) which has not yet been found in the coccidium of the rabbit (this stage is nevertheless very general in the coccidian world) and a very peculiar flagellated stage. (Fig. 6, d.) The absence of this latter stage in the coccidium of the rabbit cannot be ad-

vanced as an objection to the relation of the parasite of malaria to coccidia, inasmuch as amongst incontestable coccidia (coccidium of the intestine of salamandra maculata) there are examples of the flagellate condition.

Fig. 6.—Parasite of malaria: a, amœboid stage; b, spherical form c, crescent; d, flagellate form.

On the other hand, true spores, provided with a protective covering, have not yet been seen in the parasite of malaria. It is more than probable, however, that these spores do exist in Nature, and that it is in this resistant condition that malaria invades the human organism. That disease has this in common with the coccidiosis of the rabbit that it represents a miasmatic disease of the most typical kind.

It is unquestionable that carcinomata also approximate to the category of miasmatic affections. Although less pronounced than malaria or goitre, the endemic character of cancer is still a fact that has often struck observers. The frequency of these malignant tumours is far from being equal in all countries. By the side of regions of the globe which are exempt, or very nearly so, from this disease (Farö Islands, etc.) there are others where carcinomata are very common. But besides this feature which they have in common with coccidian diseases, carcinomata present another. As is the case in the coccidiosis of the rabbit, carcinomas are distinguished by an exaggerated proliferation of the epithelial cells of the affected organs. It is precisely this character which struck M. Malassez when he made his researches on the coccidian nodules of rabbits. The fact that in this instance the epithelial neoplasia was of unquestionably parasitic origin suggested to M. Malassez the hypothesis that carcinomata might possibly be tumours caused by the parasitism of one or other of the sporozoa.

Numerous attempts made with the object of discovering pathogenic bacteria in carcinomata have, in spite of the assertions of MM. Scheuerlen, Koubassoff, and others, had nothing but purely negative results. This failure supplied another indirect indication that carcinomata might be due to the parasitism of microbes other than bacteria.

The question of the parasitism of tumours was in this incubation stage when M. Darier,⁵ a fellow worker of M. Malassez at the Collège de France, discovered some very peculiar cells in a case of Paget's disease (a disease of the skin related to cancer) in the very middle of the elements of the swollen epithelium. M. Malassez assigned to these cells, which were apparently foreign to the human organism, a place amongst the sporozoa. M. Darier's discovery was soon followed by that of M. Albarran⁶ (a pupil of M. Malassez), who saw some parasitic cells in a case of cancer of the jaw. Not long after a whole literature came into existence on the parasites of skin diseases (Darier's follicular psorospermosis, Paget's disease), and especially of carcinomata. MM. Darier, Wickham, Vincent, in France; Thoma, Sjöbring, Henxelom, in Germany; Kossinsky, of Warsaw, contributed to elucidate this difficult question of the parasitic etiology of epithelial tumours. The first results were on the whole encouraging in the direction of the discovery of sporozoa, especially some connected with the family of coccidia as the causes of carcinomata and certain skin diseases. But this period of perhaps rather exaggerated optimism was quickly followed by a scepticism not less extreme. A whole series of observers, who have tested the statements of the authors above mentioned, have pronounced themselves against the discovery of coccidian parasites in

⁴ *Zeit. für die Protizoen-Forschung*, Berlin, 1892.

⁵ *Comptes Rendus de la Société de Biologie*, April 13th, 1891.

⁶ *Semaine Médicale*, 1899, p. 117.

tumours. These pretended parasites are, according to them, nothing but degenerated cells of the tumours themselves. In France, MM. Borrel, Cazin, Duplay, Fabre-Domergue, and in Germany Klebs, Ribbert, Schutz, and many others have expressed this view. The spirit of scepticism soon gained ground to such an extent that several authors considered the question of coccidia in tumours as dead and buried. Some observers, however, such as M. Stroebe and M. Steinhaus, were less positive in negation, and expressed the opinion that, in addition to degenerated cells, there might possibly also exist true parasitic forms. The general interest in the question became so keen that in almost every laboratory the study of this subject was commenced with great zeal. There followed a whole series of publications, which form the last period in the study of the parasite of tumours. I propose to devote a special chapter to them, dwelling almost exclusively upon the carcinomata.

3. It is unquestionable that among the authors cited many have seen, besides all kinds of degenerated cells, fragments of nuclei, etc., substances foreign to the carcinomatous cell; but inasmuch as, owing to the complexity of the phenomena, and the fact that malignant tumours have been especially studied by pathologists, it is extremely difficult to form an exact idea from the descriptions, I shall particularly follow the drawings given by the authors.

It is beyond question that in the plate given by M. Sjöbring⁷ of Lund, in his dissertation on the parasite of carcinoma, there are, side by side of forms which have certainly nothing in common with this parasite, others which belong to the microbe of carcinoma. These are, in the first place, small round bodies lodged in the protoplasm of the carcinomatous cells, and in the second cells filled with analogous round bodies. These are, I believe, speaking generally, the first forms in which cancer parasites can be recognised. There is, however, so little clearness in M. Sjöbring's description of his preparations that great hesitation must be felt in interpreting them in a precise manner. It is in a case of cancer of the breast that M. Sjöbring has found most of the forms described by him.

In another case of the same form of new growth M. Foà⁸ of Turin satisfied himself as to the presence of round bodies lodged in cancerous cells. He gives illustrations of them, in which foreign elements enclosing a small nucleus and foreign appendages in the form of rays can be distinguished in the cancerous cells. M. Foà is quite ready to admit the parasitic nature of these bodies.

The same forms have been found again by M. Soudakewitch⁹ in a large number of cases (more than fifty) of different carcinomata. They were especially abundant in a primary cancer of the pancreas and in the metastasis of its lymphatic glands. The cancerous cells were literally stuffed with parasites, which presented themselves sometimes in the form of very small round cells, lying close beside the nucleus of the cancerous cell, sometimes in the form of large oval bodies furnished with a thick covering, and recalling the full-grown coccidia. M. Soudakewitch's description and illustrations leave no doubt that in his case we have not to deal with any products of the degeneration of cell or nucleus. The bodies described by him have entirely the appearance of cells foreign to the human organism, and bear the closest resemblance to sporozoa, notably coccidia. In a second paper, M. Soudakewitch¹⁰ has described the same bodies in a number of other cases of carcinomata of different kinds.

The important discoveries of M. Soudakewitch have not failed to meet with many objections. M. Fabre-Domergue¹¹, in a note presented to the Société de Biologie, declared that M. Soudakewitch's parasites were nothing more than pseudococcidia, and were in reality the results of cell degeneration, which, as in the case of other bodies, have been taken for parasites of tumours.

Confirmations, however, of the discovery were much more numerous than criticisms. M. Foà¹², in a later paper, again described the same parasitic bodies in several cases of cancer. M.

Borrell¹³ found parasitic bodies, altogether like those described by MM. Foà and Soudakewitch in true epitheliomata. M. Borrell's testimony is all the more valuable that he was formerly opposed to the views of the authors who uphold the presence of parasites in cancer. He has succeeded in clearly distinguishing the degenerated and modified cells so frequent in epitheliomata from the bodies which can be regarded as intruders of foreign origin.

Another confirmation came from England. Two scientists, MM. Ruffer and Walker¹⁴, found the same parasites in a large number of carcinomata, amongst others in a case of metastatic carcinoma of the liver. Their preparations, coloured with Biondi's mixture, bring out the parasites with all clearness that could be desired. The coccidia, stained a light blue, enclose a dark brown nucleus, the cancerous cell is stained a dirty yellow white, its nucleus takes a green tint. Like M. Soudakewitch's preparations, those of MM. Ruffer and Walker show a whole series of stages of development, starting from tiny round bodies enclosing a nucleolus up to oval forms which occupy the whole of the carcinomatous cell.

M. Sawtchenko,¹⁵ of Kieff, who in his first essay (produced in collaboration with M. Podwyssotski) only saw indistinct forms, has, in a second publication, been able to confirm the observations of M. Soudakewitch and to find the same parasite.

Doubt is therefore no longer possible. In a large number of different carcinomata there have been found lodged in the protoplasm of the cancerous cells round bodies, having the structure of true cells and presenting no appearance of degeneration either of the protoplasm or of cell nuclei.

It now remains for us to examine these bodies a little more closely in order to determine their nature and their relations with other analogous productions.

4. In scraping a little carcinomatous tissue from any organ—for example, the mammary gland—and on examining it in aqueous humour, or in some other unaltering liquid, with high powers, there will be found in a certain number of carcinomatous cells small round bodies, sharply defined (Fig. 7). Lodged in the interior of the protoplasm, these bodies present the closest resemblance to the coccidia of the rabbit in its early stages of growth, as one may convince oneself by comparing the two formations (Figs. 4 and 7)

Fig. 7.—A cancer cell with its parasite in cancer of the breast; n, nucleus; p, parasite.

Like the young coccidia of the rabbit, the round bodies of carcinoma grow in the interior of the cells. In preparations of these tumours may be seen a whole series of stages of growth; the small round bodies grow and become more and

Fig. 8.—Cancer cells with two parasites; after M. Soudakewitch. more defined by reason of the development of their membrane (Fig. 8). The same thing may also be seen in a striking manner in the liver of a rabbit infected with coccidia.

⁷ Fortschritte der Medicin, 1890, p. 529, Pl. iv.

⁸ Gazzetta Medica di Torino, 1891, n. 36.

⁹ Annales de l'Institut Pasteur, 1892, mars, p. 145, pl. v. to vii.

¹⁰ Ibid., août, p. 545, pl. xi-xii.

¹¹ Comptes Rendus de la Société de Biologie, 1892.

¹² Gazzetta Medica di Torino, 1892, p. 381.

¹³ Evolution cellulaire et parasitisme dans l'épithélioma, Montpellier, 1892.

¹⁴ BRITISH MEDICAL JOURNAL, July 16th, 1892, p. 113.

¹⁵ Centralblatt für Bakteriologie, T. xi., 1892, p. 493.

It sometimes happens that a cancer cell contains several parasites pressed one against the other (Fig. 9). The same phenomenon may also be seen in the coccidium of the rabbit. "Very often," says M. R. Pfeiffer, "an epithelial cell contains five or more young coccidia. The parasites are in that case pressed so closely together that they assume a polyhedral form."¹⁶

The structure of the round bodies of carcinomata presents the closest resemblance to those of the coccidia of the rabbit in the different stages of their development. In both cases there is to be seen a cellular membrane which becomes thicker and thicker, and protoplasmic contents which stain with difficulty, and a large nucleolus which fills the transparent nucleus.

Fig. 9.—A cancer cell full of parasites; after M. Soudakewitch.

The striking analogy between carcinomata and the coccidiosis of the rabbit extends also, as has already been said, to the anatomical lesions of the organs. The epithelial vegetations of the intestine and liver of the rabbit can especially be compared to the adenocarcinomata—that is to say, to epithelial tumours which still keep the glandular type. One has only to glance at the two figures here given (Figs. 2 and 10) to be struck by the resemblance between hyperplasia of the bile ducts of the rabbit attacked with coccidia and adenocarcinoma of the rectum in man.

Fig. 10.—Adeno-carcinoma of the rectum in man; after M. Ziegler.

As compared with these analogies, the differences are not of sufficient importance to be advanced as negating the fact that carcinomata are allied to coccidia. The latter do not produce true metastases. But there are also cancers which never, or very rarely, produce metastases, and this does not prevent their being intimately allied with other cancers.

Up to the present a much more limited number of stages have been noticed in cancer than in coccidia. That is unquestionably a great obstacle to a definitive judgment being formed on the subject. But it must not be forgotten that the study of parasitism in carcinomata is only beginning. The coccidia of the rabbit have been known for half a century, and it is only quite recently that, thanks to the important researches of M. R. Pfeiffer, the endogenous formation of the falciform bodies has been discovered. The finding of new stages in carcinomata need not therefore be despaired of.

Several pathologists who have lately occupied themselves with the question of parasitism in carcinomata have believed they could fill this gap. Thus MM. Stroebe, Podwysotski, and Sawtchenko, and quite recently M. Soudakewitch, have discovered falciform bodies in several cases of cancer. From all that I have been able to observe up to the present, as well as from all the statements of the authors whom I have just quoted, the formations taken by them for falciform bodies, or

(what is the same thing) for stages of the crescent, can in no way be compared with the corresponding productions of coccidia or of sporozoa in general. The true crescentic bodies, as, for example, those of M. Laveran in malaria, are distinguished by the regularity of their outline, by the close resemblance to each other of the individual bodies, and by a number of details which are wanting in the pseudo-crescents of carcinoma. In order to satisfy himself as to this difference, I ask the reader to compare the two illustrations here given (Fig. 11, *a*, *b*), one of which (*b*) represents the true crescents of a coccidium, and the other (*a*) the formations taken for crescents in cancer. I look upon the latter as chromatic forms of the nucleus of cancerous cells. They may be

Fig. 11.—*a*, Pseudo-crescents in a carcinomatous cell (after Podwysotski and Sawtchenko); *b*, true crescents of a coccidium, Klossia (after Balbiani).

Fig. 12.—Pseudo-coccidium; after L. Pfeiffer.

designated as pseudo-crescents, just as in cancers (especially in epitheliomata, it is necessary to distinguish pseudo-coccidia (Fig. 12), so often confounded with formations really analogous to sporozoa.

In spite of the impossibility of admitting the presence of falciform bodies in carcinomata, and in spite of certain other differences which still exist between these tumours and coccidiosis, it cannot be denied that the round bodies so often found in carcinomata present, according to what is at present known, the closest analogy with coccidia. Although the last word has not yet been said on this subject, this conclusion may already serve as a starting point for many new researches.

When it is borne in mind that the coccidiosis of the rabbit is not contagious, the failure of so many attempts at the inoculation of carcinomata will easily be understood. On the other hand, the cases of contagion recorded in literature, as well as some positive results in the experimental transmission of cancer (those of M. Hanau, in his cancer of rats, and M. Wehr, etc.), might be explained by the presence of stages developed on the surface of the organism attacked. It is known that the miasma of the coccidiosis of the rabbit (that is to say, the spores of the parasite) are formed outside the organism, but are to be found in the closest neighbourhood to these animals.

Malaria may be cited as an example to show how little infectious is the character of these coccidian diseases. In birds, in which malaria is extraordinarily frequent, contagion by blood containing parasites has never been effected in a really conclusive manner. It is, therefore, quite natural that cancers should present a miasmatic rather than a contagious character.

From the summary given in this article it will be easily seen that the microbiostudy of carcinomata is still in its infancy. But it will also be seen that the beginning which has already been made is encouraging, and that in order to arrive at a solution of the problem it is desirable that pathologists should join their forces with those of zoologists well versed in the science of sporozoa.

A HOME FOR CHOLERA ORPHANS IN ST. PETERSBURG.—The home for children whose parents have died of cholera, which was recently established in St. Petersburg, has been moved into roomier premises, where there is accommodation for forty children. The number of children now in the home is twenty-three.

SUCCESSFUL VACCINATION.—Dr. J. J. Rutherford, Medical Officer for the No. 7 District of the North Brierley Union, has received a grant for efficient vaccination.

¹⁶ *Centralblatt für Bakteriologie*, T. xi, 1892, p. 6.