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The Parasitic Theory of the Ætiology of Carcinoma.

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THE PARASITIC THEORY OF THE ÆTIOLOGY OF CARCINOMA.*

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In any discussion on cancer the question of its ætiology should always take precedence of that concerning its treatment, since the latter, to be both rational and effective, should be based upon the former. It is not my purpose at present to consider the numerous theories put forward in time past to explain its essential cause, but rather to invite your attention to a *résumé* of the latest and perhaps most fascinating explanation offered as to the prime cause of this dreadful malady.

Just who is entitled to the credit of having first advanced the hypothesis of its parasitic origin it would be hard to tell, but to two English surgeon-pathologists, Hutchinson and Paget, we are largely indebted for having advanced the *a priori* plausibility of such a view. In a

* Read before the Medical Society of the State of New York at its eighty-seventh annual meeting.

memorable address some years ago the latter called attention to the parasitic origin of most of the xylomata or woody tumors seen on so many trees, and ventured the prediction that an analogous parasitic origin would ere long be determined for many of the tumors met with in the animal kingdom. That we now have a class of infectious granulomata, acknowledged by all, is not yet sufficient realization of such a prophecy.

Virchow recognized as early as 1847 certain peculiar bodies noted in and between carcinoma cells, which he then supposed to be evidences of degeneration. Their true nature was not made out till 1888, when they were identified as belonging to the sporozoa, although he himself later (Virchow's *Archiv*, Bd. xxxiii) suggested the possibility of their being psorosperms.

Inasmuch as the present paper deals mainly with these organisms, it will be proper to stop here a moment to rehearse a few statements concerning their nature and place in the animal kingdom. First of all, they are distinctly *not bacteria*, which are *vegetable* organisms, but belong to the *protozoa* or unicellular *animal* forms.

The *Gregarinidæ* are included in the suborder *Endoplastica* and subclass *Sporozoa*, according to Leuckart, and are described as having ovoidal or spheroidal bodies, sometimes with a segmental constriction, occasionally with one end beaked and carrying horny spines. They consist of a dense ectosarc and a softer endosarc, containing an endoplast but no contractile vacuole. They are all essentially parasitic. They have neither oral aperture nor pseudopodia. They contain granular protoplasm with nucleus and nucleolus, and vary in size even up to a centimetre in diameter.

The *Coccidia* form another subclass of the *Sporozoa*, are quite similar to the foregoing, but have a micropyle at one end.

According to another classification, the *Sporozoa* or *Cytozoa* are divided into four subclasses, as follows: *Gregarinidea* (by some held to include the coccidia); *Coccidiidea* or *Microsporidia; Myxosporidia; Sarcocystidia* or *Sarcosporidia.*

But minutiæ of classification aside, it is enough for our present purposes that the bodies in question are exceedingly minute forms of unicellular animal life. In 1878 Rivolta (*Dei parassiti vegetali*, Turin, 1878) and Bollinger (Virchow's *Archiv*, Bd. lviii) recognized their parasitic nature and identified them as *Gregarinæ;* and they gave to the lesions found in fowls and pigeons which so closely resemble molluscum the suggestive name *epithelioma gregarinosum.* In 1880 Nedopil, Herisson, and others thought to characterize miliary carcinomatosis as an infectious disease. Neisser, in a study of molluscum contagiosum (*Vierteljahrschft. f. Dermatol.*, 1888, xv, 553), distinguished between their spores and better developed stages. He only studied them in sections, his culture and inoculation experiments failing. He found them in greatest number in affected tissues, but also in uninjured cells and adjacent tissues.

L. Pfeiffer described, also in 1888 (*Zeitschft. f. Hygiene*, 1888, iii, 3, and iv, 422), certain bodies met with in two cases of general carcinosis and one of sarcoma of the breast, and regarded them as belonging to the *Sporozoa.* He found them in the epithelial cells of a fresh, warm melanotic growth, and, studying their developmental stage, saw that it resembled closely the spore formation of the *Microsporidia.* (See also *Die Protozoen als Krankheitserreger*, Jena, 1890.)

Darier, in 1889, observed certain bodies which he believed to be coccidia in a hitherto undescribed skin disease to which he gave the name *psorospermose folliculaire végétante* (*Annales de derm. et de syph.*, 1889, No. 7), and later,

with Wickham (*Ctrlbl. f. path. Anat.*, i, 682), he attributed Paget's disease of the nipple to a coccidium which invades the skin.

It would certainly seem as though, provided Paget's disease of the nipple is a factor in the production of certain mammary cancers, and that it is a true psorospermosis, the best conditions for a study of the parasitic nature of cancer would be met with in cases of this disease.

Hutchinson, Jr. (*Trans. of the Path. Soc. of London*, xli, 1890, 214), and Wickham (*Archives de méd. expérimentale*, 1890, i, 1; *Annales de dermat. et de syph.*, 1890, i and ii) have both studied the matter carefully, the latter with seven cases. Wickham describes three stages of the disease after invasion:

1. Thickening and disorganization of the epidermis and inflammation of the corium.

2. Elevation of the horny cells, lively escape of leucocytes which crowd aside the epithelial cells, proliferation of the rete mucosum, and the epithelium of the sweat, sebaceous, and milk glands, and finally extensive infiltration of the cutis.

3. Stage of true carcinomatous growth from both the superficial and glandular epithelium.

In the beginning the parasites appear with or without nuclei, later surround themselves with a double membrane, while the contained protoplasm differentiates itself into a number of granules, and thus is formed what he calls a sporiferous cyst. These he found not only in the epidermis, but also in various gland ducts and in the pearly bodies. In spite of failure to cultivate or inoculate, Darier and Wickham did not doubt their parasitic as well as their pathogenic character, and felt that under their influence not only epithelioma but other forms of carcinoma might develop.

Malassez and Albarran found in two epitheliomata of the jaw peculiar bodies having striking resemblances to the coccidia so often found in the livers of rabbits (*Soc. de biol.*, April, 1889), and Vincent had a similar experience (*Annales de micrographie*, 1890, ii, p. 10).

Thoma found in the nuclei of many cancer cells peculiar bodies so different from other human cells that he considered them parasitic and thought they might be encapsulated coccidia (*Fortschrit. d. Med.*, 1889, p. 413).

Sjörbring, of Lund (*ibid.*, p. 529), studied their life history and found free extracellular as well as intracellular and spore forms, and called attention to their resemblances to the organisms which produce *pebrine* in silkworms.

Steinhaus examined thirty cancers from various sources, sometimes finding these bodies, sometimes not, but considered them parasitic when present (Virchow's *Archiv*, Bd. cxxvi, p. 533).

Hacke described in 1890 four cases of cancer in which he found coccidia in and among the cells, varying in size from two to fifty microns, the smaller intracellular the larger extracellular, spherical, encapsulated, the capsule very highly refractive. Within the cell they often appeared as in a vacuole, owing to the shrinking of the surrounding protoplasm during hardening. As they grew they seemed often to fill and destroy the cell (*Soc. de biol.*, Nov. 8, 1890).

Van Heukelom, of Leyden, studied some two hundred tumors, and came to conclusions essentially those of Thoma and Sjörbring (*Ctrlbl. f. path. Anat.*, 1890, p. 704).

But these views were not accepted without lively dispute. Russell, Piffard, Schütz (*Microscopische Carcinombefunde*, Frankfort, 1890), Török, and Tommasoli, among others, after minute study claimed that these so-called coccidia were only altered cells, simple masses of chromatin, products

of degeneration, etc. Klebs made implantation experiments without success, and these bodies underwent no change or increase. Duplay and Cazin, finding no such changes as they thought coccidia in their evolution should evince, concluded these bodies to be of degenerative origin and to result not only from cells but from mitoses.

Ribbert made a most exhaustive study (*Deutsche med. Woch.*, 1891, p. 1179) of cell inclusions in cancer, and concluded that his results did not permit his acceptance of the parasitic theory, and therefore held to the degenerative view of their nature.

Ramsay Wright (*Ctrlbl. f. allgem. Path.*, 1890, No. 11) and Russell (*Brit. Med. Jour.*, 1890, p. 1297), while not so opposed to the parasitic view, referred these bodies to the saccharomyces. Moreover, the latter found among them certain granules which have an affinity for fuchsin, the so-called "fuchsin bodies" (Fuchsinophile), which are also to be found in other pathological and normal tissues.

Cornil (*Journal de l'anat. et de physiol.*, 1891, No. 1) and Hansemann (Virchow's *Archiv*, Bd. cxxiii, p. 356, 1890) think it possible to mistake for coccidia or their spores various stages of karyokinetic cell division.

Stroebe (Ziegler's *Beiträge*, 1891, xi, Hft. 1) and Steinhaus (*Ctrlbl. f. allgem. Path.*, 1891, No. 2) feel compelled to admit the sporozoan nature of these bodies, but are not convinced that they are the true cause of cancer.

Sudakewitsch (*Wratsch*, 1891, No. 49) decides that "a carcinomatous growth of epithelium in man, as well as in other animals, may follow the immigration of parasites belonging to the *Sporozoa*" (*Med. News*, Jan. 7, 1893, p. 20).

While all these studies concerning coccidia were in progress the bacteriologists were by no means idle. Even in 1887 Scheurlen published his address on the ætiology of

cancer (*Deutsche med. Woch.*, 1887, No. 48, p. 1033) and described a small spore-bearing bacillus, slightly motile, easily stained, bleached by alcohol, but shown by Gram's method and its spores by the ordinary stains. He found that it grew on agar, on potatoes, and in broths. This bacillus was difficult to find in sections, and its spores were found in only about one cover-glass preparation of cancer juice out of three. He also described the appearance of the spores in unstained preparations in words which almost make one who reads them now think he mistook coccidia for spores. But he cultivated his bacillus and injected it into the mammary glands of dogs and found, as a result, tumors whose most notable characteristic was cell proliferation.

His claim to priority, by the way, was hotly contested by Freire (*Deutsche med. Woch.*, 1888, No. 1, p. 14).

In a discussion following the reading of Scheurlen's paper, A. Fraenkel expressed himself as believing that cancer was a parasitic disease, but that its prime cause might belong to a class of organisms then little or not at all known, and not bacteria.

In a critique on the so called cancer bacillus Baumgarten makes some very sensible remarks, which should be carefully noted by those interested in the subject (*Jahresbericht der Mikroorganismenlehre*, 1887, iii, p. 273). He holds that cancer, like all true tumors, is an abnormal condition of original embryonal elements, according to views enunciated by Cohnheim, and that, according to these, there is neither need nor room for a bacillus. He argues that we have as much reason to expect, *e. g.*, a *teratoma bacillus*. Or, supposing that this theory be held only to concern a certain number or proportion of cases, he still regards the hypothesis as untenable, since it has no analogies either in pathological mycology or parasitology. For, so

far as we know, he maintains, all other micro-organisms cause, instead of cell and tissue proliferation, rather exudative inflammation and tissue necrosis, the later proliferation being protective when present.

I may, perhaps, be permitted here to digress for a moment to give an illustration of the way in which Cohnheim's views may be made to suit any purpose. The writer of an editorial in a recent number of the *Journal of the American Medical Association* (Jan. 14, 1893, p. 49) epitomizes them to this effect: that they constitute a theory that "tumors are due to exaggerated growth of primary remnants of embryonal folds gone astray in various parts of the body," and states that it has been severely criticised by enthusiastic believers in the parasitic origin of carcinoma, although so good a bacteriologist as Baumgarten, as just stated above, falls back on it as an *a priori* argument against this origin. But this same writer goes on to say that it has been shown that embryonal folds exist in all multicellular organisms, and that, consequently, invertebrates would theoretically be just as liable to various forms of tumors as the higher animals; "*but such a thing as carcinoma has never been described in the inferior animals up to the present time, although they are very liable to parasitic tumors of various kinds.*" (Italics mine.) Here he shows a lamentable lack of knowledge, since veterinary and pathological records and museums are full of instances such as he denies, while that prince of comparative pathologists, J. Bland Sutton, has described numerous specimens which have come under his own observation. Hence the force of such argument is at once lost.

Scheurlen's position was also speedily attacked from other quarters—by Senger, A. Pfeiffer, van Ermengem, Rosenthal, Sanquirico, and Sanarelli (*Riforma med.*, 1888) —all of whom insisted that his cancer bacillus was widely

diffused and harmless, while Rosenthal showed that it frequented the nipples of healthy women and young girls.

Schill, who worked at this subject for six years, observed something which he described as consisting of two colored (stained) points connected by a hyaline body, which he found in large numbers in various cancers, and which he cultivated and considered a fungus (*Deutsche med. Woch.*, 1887, No. 48, p. 1034).

A little later Nepveu (*Gazette hebdom. de méd. et de chir.*, 1888, No. 18) found all sorts of organisms in breaking down and ulcerating cancers; and Hauser (*Münchener med. Woch.*, 1888, No. 12) and Markara (*Deutsche med. Woch.*, 1888, No. 31) contested Scheurlen's hypothesis on pathological grounds.

Scheurlen, however, rejoined (*Deutsche med. Woch.*, 1888, No. 30), with the aid of Francke, Lampiasi-Rubino, and Magalhaes, and fought for the acceptance of his contentions, but apparently in vain, since to-day they are nearly forgotten. Fatichi (*Il bacillo di Scheurlen è un saprofita della pelle*, Firenze, 1889) cultivated from skin of normal individuals a bacillus which morphologically, in cultures, and in every other way, resembled Scheurlen's. It is also identical with Bordoni-Uffreduzzi's *Bacillus epidermidis.*

On the other hand, Koubassoff professed, in 1890 (*Ctrlbl. f. Bakteriol.*, vii, 317), to have found in cancerous tumors a bacillus different from Scheurlen's, which, when implanted in animals, caused disseminated nodules, histologically resembling cancer, and final death. No one seems to have confirmed his researches.

Balance and Shattuck (*Proc. of the Royal Soc.*, xlviii, 1890, p 392) reported only failures to find any organism in cancers (also *Brit. Med. Jour.*, 1887, Oct. 29, p. 929). Since

1890 scarcely an article has appeared on the subject of cancer bacilli, and the attention of all workers in this field seems to have been concentrated on the *Sporozoa* which are alleged to cause the disease.

Inasmuch as everything now points in their direction, it will be worth while to refer briefly to methods for their detection. Pieces of cancer tissue should be preserved in Flemming's solution, which seems to cause the organisms to appear to better advantage. The stain which gives the best result is the so-called Ehrlich-Biondi triple stain, whose formula is simple, but whose happy combination seems difficult. The directions given are to dissolve—

Methyl green 0·5 in distilled water.... 100;
Acid fuchsin 0·5 in distilled water.... 40;
Orange 2·0 in distilled water..... 200.

These solutions to be mixed and filtered before use. Sections are left in it for twelve hours, then washed, dehydrated, cleared, and mounted. With this stain the nucleus of the cancer cell becomes green, the protoplasm orange-red, the nucleus of the parasite red, and its protoplasm light-blue. Working with it, Puffer, Walker, and many others have not hesitated to pronounce the included bodies to be true parasites.

At a meeting of the London Pathological Society held December 20, 1892 (*Lancet*, December 31, 1892, p. 1496), Jackson Clarke described a case of epithelioma of the nose which abounded in unmistakable psorosperms. To be sure, coccidia with stain-resisting capsules were not found, but every other stage of rabbit's coccidia was represented. The idea of degeneration was negatived by beautiful nuclear figures and by clear evidence of biological processes. Conjugation and amœba formation were observed. Many large psorosperms lay within the epithelial cells, whose capsules were seen to possess perfect radial striation. He called at-

tention to the fact that most writers had failed to distinguish the amœbæ from leucocytes, and stated that the amœboid stage of the parasite's cyclic existence afforded the *key to the malignancy of cancer.* He had found clear evidence of the following processes:

1. A single psorosperm, or one formed by conjugation of two, becomes changed by formation of a reticulum which extends outward from the nucleus till it fills the whole cell.

2. The reticular plasmodium, usually surrounded by a capsule, consisting of the dead and distended host cell, breaks up into rounded segments which keep the reticular structure, and stain faintly purple with acid hæmatoxylin.

3. Within some of these daughter psorosperms fine filaments of chromatin appear. By breaking up of the same, amœboid cells are set free, which multiply by division and are distinguished from leucocytes by treatment with acid hæmatoxylin.

4. These amœboid bodies make their way in vast numbers into connective-tissue spaces beyond the epithelial part of the growth. In passage they separate epithelial cells and thus facilitate epithelial down-growth and detachment of small groups of cells. A considerable degree of inflammation is caused by this tissue invasion, with results similar to those seen in inflammatory papilloma (*e. g.*, mucous tubercles)—*i. e.*, extension of epithelial growth, new formation of vessels, etc.

5. Later most of the amœbæ disappear and the resultant inflammation subsides. A small proportion enter epithelial cells and can there be detected, with care, even in their non-nucleated stage. Those that remain are by this time the somewhat familiar intracellular psorosperms, most abundant in and about cell nests. Arriving at a certain stage, the cycle is renewed and a fresh extension of growth takes

place, sometimes with detachment of venous or lymphatic emboli and resulting metastasis. Clarke insisted that the cyclic life of these parasites and their reaction on the tissues could account for all the phenomena of cancer.

He remarked further that these amœboid sporozoa were identical in structure with some of the plasmodia met with in ague. The cyclic cause of the disease corresponds with the cyclic life of the parasites. From a psorospermosis of the spleen and lymph nodes it is but a step to leucocythæmia and sarcoma. In a cystic scirrhus he had found the cream-like contents of the cyst to consist wholly of amœboid psorosperms. Apart from the mystery of the path (and source) of infection, the nature of the disease is now revealed.

During the discussion following Clarke's remarks Mr. Shattuck said that though the former had described one cycle of growth in man, it was quite possible to have another and differing cycle outside the human organism—*e. g.*, in rabbits, where the appearances were often different. He himself inclined to the view held by Metschnikoff. We can not infect lower animals with cancer from human beings, but are seeking now how to cultivate the parasite and then inoculate animals with it. Instances of successful inoculation are at present as rare as the occurrence of cysticercus in man.

That indefatigable worker, Metschnikoff, has recently taken part in this discussion by an argument entitled Remarks on Carcinomata and Coccidia (*Revue générale de sciences pures et appliquées ; Jour. of the Am. Med. Assoc., loc. cit.*). He states that these so-called parasites have the greatest analogy with the coccidia; he contrasts carcinoma with coccidiosis of rabbit liver, and sees between them many points of striking similarity. Coccidiosis is an infectious

parasitic disease, not contagious, its lesions nodular in arrangement, composed of proliferating epithelium of biliary ducts, the cells containing the parasites or *Sporozoa* whose *rôle* is now not denied. So, too, epithelioma is characterized by epithelial proliferation; is not contagious, is nodular, and its cells contain peculiar bodies which certainly present most accurate resemblances to *Sporozoa*, and he concludes the researches reported to be sufficiently reliable to serve as a starting point for new studies.

The most elaborate contribution to the subject is that of Podwyssozki and Sawtschenko, of Kiev, entitled Parasitism in Cancer, with Description of Certain Parasitic Organisms found in Cancerous Tumors (*Ctrlbl. f. Bakteriol.*, 1892, xi, pp. 493, 532, 559). In their monograph they have considered at length the history of the subject. They also call attention to the fact that a multitude of analogies offer where epithelial proliferation is due to the irritation produced by parasites—*e. g.*, besides the changes in the rabbit's liver due to the *Coccidium oviforme*, the lesions in the intestinal mucosa of many animals, with inflammatory infiltrate and neoplastic growths caused by the *Coccidium perforans*. (Full details of these and similar lesions are to be found in L. Pfeiffer's *Die Protozoen als Krankheitserreger*.) To even summarize their most interesting paper would be to exceed the limits of this one; but some of their statements must be here epitomized or quoted. For example, this: "The more pronounced the intensity of carcinomatous proliferation, the more numerous the mitoses in the cancer cells; the softer the tumor and more marked its tendency to degeneration, the greater the number of parasitic organisms in its cells. They are best to be found in medullary growths, and especially in those of the breast; in epitheliomata of the lips and face they do not abound."

They studied these sporozoa in more than twenty cases of miscellaneous cancers, and looked carefully to find in them the same biological characteristics that are found in bodies whose protoplasmic life history is unquestioned, such as evidences of cell division, holding that the dispute concerning their true nature, as illustrated by the papers of Steinhaus and Stroebe, was due to the failure of previous investigators to produce convincing evidence thereof. They find the sporozoa either inside the cells or in the intervening lymph spaces, and furnish some beautiful chromolithographic reproductions of their specimens. These bodies consist of cyst-like cells (sporocysts) with semilunar nuclei, which undergo fission, their progeny escaping and becoming disseminated by the lymph paths.

They consider it probable that the parasites display a symbiosis or commensalism with the epithelial cells. They leave open the question of just what part the coccidia play in the ætiology of cancer, declining to express convictions until inoculation experiments with cultures shall be made possible. (The experiments of Delepine, *Brit. Med. Jour.*, May, 1891, make it probable that this happy day is not far off.) That we have here to do with a true parasitism they do not doubt. Or, to put it in their own words, "In a question of such extreme difficulty, so acknowledged by zoologists and specialists, as the determination of species of sporozoa, it will be the most sensible thing to 'go slow' (*zurückhalten*); for the immediate present it is enough if we can ascribe them their proper place."

Finally, Foà, of Turin, described and figured, in August of last year (*Ctrlbl. f. Bakteriol.*, 1892, xii, No. 6. p. 185), certain bodies found in and about cancer cells which stained with hæmatoxylin and showed marked variations in size and configuration, whose evolutionary phases, appearances, segmentation, and behavior to stains all stamped them as

parasites. He, however, hesitated to insist that their presence was more than accidental.

Foà's publication, in which he criticised some of Podwyssozki's statements, has provoked a very recent rejoinder from the latter, in which he reiterates his former statements and views, and promises further corroborative evidence in the near future (*ibid.*, No. 16, p. 551).

Herewith is concluded a necessarily incomplete, because brief, summary of our present knowledge bearing on one of the most important topics now or ever before our profession. While the parasitic theory is by no means new, the facts which tend to substantiate it are of very recent discovery—so recent, in fact, that it would be unseemly to accept them as all-sufficient. Obviously they can but constitute a mere foundation upon which we may hope to build. The other all-important yet subsidiary topics of the geographical distribution of cancer, and the influence of sex, age, part involved, civil and sanitary condition, injury, heredity, state of nutrition, and of preceding benign growth, must be constantly borne in mind. Many apparent contradictions must be explained, many conflicting statements reconciled.

The proper position for the real student, it would seem to me, is in the middle ground, between skepticism on the one hand and credulity on the other, working and waiting for the light that we have great reason to eagerly expect, and probably from the direction indicated in the course of this paper.

For my own part, I can not help feeling that we are on the eve of great discoveries in this matter, partly, perhaps, because I have for years had a growing conviction that cancer—and syphilis, too—were parasitic diseases, due to either unfamiliar or yet unknown organisms, and that some new technical method, or some new application of old methods,

would ere long furnish the key to the mystery. Whether we have been recently supplied with this by the investigators quoted above is as yet uncertain, though probable. How anxiously impatient, yet sanguine, I am you may better appreciate when you recall that my home is (in western New York) in a limited area, where the death-rate from cancer is greater than in any other part of our continent.