CHAPTER VIII

THE PARASITIC THEORY

The parasitic theory is the oldest hypothesis of the origin of cancer. It appealed to the ancients, was tacitly accepted throughout the Middle Ages, was definitely argued by modern observers, and reached the height of its popularity as a scientific theory about 1895, but during the last fifteen years it has rapidly lost ground, and today few competent observers consider it as a possible explanation of the unknown element in blastomatosis.

The data concerning the parasitic theory fall into four main classes: (1) Studies of the incidence of cancer; (2) the search for specific parasites in tumors; (3) the experimental production of tumors; (4) theoretical consideration of the nature of cancer.

The Incidence of Cancer.—In 1809 Arnaudet reported that in certain rural districts in Normandy during a period of eight years, the cancer mortality reached 14.88 per cent. He noted the occurrence of cancer in several members of the same household, and he concluded that the neighborhood of a cancer patient was contaminated through the water.

Many similar reports of cancer districts and cancer houses soon appeared from Guelliot, Webb, Fiessinger, D'Arcy Power, Bosc, and others. Behla found the cancer mortality of the low-lying portions of Luckau to be four times that of the central portion. He noted the frequency of cancer in the dogs of the town, the large quantities of home-grown vegetables consumed by the cancer families, and concluded that cancer is an infectious disease carried to its victims through contamination of the soil.

In 1892 Haviland from an elaborate analysis of the English census concluded that cancer is a disease of low-lying districts and of seasonably flooded riparial lands where subsoil is constantly moist, while in high dry localities it is rare.

Very minute studies of cancer localities have been made in England and other countries by numerous observers all tending to show a relation between cancer and all manner of local peculiarities; as living in "old and cancer houses" (Park), "infected streets" (Mason), houses with defective plumbing, leaky sewers (Nason), proximity to trees, especially large ones (Lloyd-Jones), collections of decaying vegetable matter, stagnant water (Poppelman), abundance of certain insects (Bosc), etc. The uncritical character of these observations hardly needs comment. Many of the fallacies involved in them have been pointed out by Sticker and by Prinzing.

At the height of their popularity, Symons showed that there were no cancer houses in Bath where cancer mortality was the highest in England. Out of this fanciful discussion Williams draws the sane conclusion that cancer is a disease of civilization, choosing its victims from the well-to-do, the well-nourished and the well-protected against infectious diseases, and that it flourishes in just the opposite conditions from those which favor the spread of tuberculosis. At one time there was a tendency to report small epidemics of cancer among men (Webb, Fiessinger), and to point out its epidemic character. Later, epidemics of cancer among cattle were described (Loeb), or among rats and mice used for breeding purposes (Gaylord, Borrel, Loeb),

for which old age and inbreeding are sufficient explanations. Bashford, in a very wide experience with captive rats and mice found no evidence of any "cage infection."

Epidemics of thyroid cancer among artificially bred trout have menaced the fish industry in several countries. Pick and Plehne concluded that it arises from overcrowding, overfeeding, and inbreeding. Gaylord demonstrated the true cancerous nature of a certain proportion of these cases, but Gudernatsch pointed out the remarkably wide distribution of the thyroid lobules in many species of fish and rendered doubtful the neoplastic character of the great majority of the "tumors." Marine and Lenhardt have shown that many of the hyperplastic thyroids regress under proper hygiene.

Statistics elaborately presented by Williams and by Hoffman show a remarkable increase in the recorded deaths from cancer during the last fifty years. In England in 1840 the cancer deaths were one in 129 of the total; in 1905 one in 17. Very similar indications are found in the records of most civilized countries (Hoffman, Lit.). Williams calculates that in England, 1900, 1 in 15 of all men, and 1 in 9 of all women, living at 35 years of age are destined to die of cancer. The increase seems to be affecting men more than women, although in England cancer is now a more fatal disease for women than is tuberculosis. The increase of cancer is concomitant with a decrease of tuberculosis.

Of the apparent increase in cancer deaths a considerable proportion must be referred to improved diagnosis. Riechelman shows for the Berlin hospitals that there was still, 1902, room for a 20 per cent. increase in the recorded deaths from cancer through improved diagnosis alone. The remaining portion must be largely referred to the longer tenure of life through immunity to infectious diseases and improved hygiene, which permit a larger proportion of persons to reach the cancer age. In Prussia, vital statistics show that the average person lives twenty-five years longer than in 1860. Willcox in a critical analysis of this subject shows that the sources of the recorded increase are quite complex, including improved diagnosis, changes in age composition of population, elimination of old age as a cause of death, improved registration, and widening of the definition of cancer.

He shows that the increase is chiefly of inaccessible cancers, among the lower classes of society, in males rather than in females, in negroes and the foreign born, and in the country more than in the cities.

The impression that cancer is actually increasing to a slight extent which cannot wholly be explained by the above factors and is more often appearing at earlier ages, is probably correct, but such a fact cannot stand as an argument for the parasitic theory.

The contagiousness of cancer was at one time supposed to be proven by clinical observation. Lusitanus (1557) claimed to have observed infection of three children by a cancerous mother. Tulpius reported the direct transfer of the disease between human beings. In the 17th and 18th centuries cancer was regarded as quite as infectious as phthisis with which it was often confounded. Lebert and Friedreich believed they had observed cancer infection of the fetuses of cancerous mothers.

The numerous observations on contact infection were supposed to point to a parasitic factor but relatively few of these cases seem to have been genuine and in these it must be held that the infecting agent is the cancer-cell. Of the many cases of *cancer a deux* reported by Budd and Guelliot none appears to be properly attested, while Demarquay found that in only one of 134 cases of cancer of the penis did the wife have cancer of the uterus, and Bossi reported that of 180 husbands of women with uterine cancer, none contracted

the disease. The attempts of Alibert, Wickham and Senn to inoculate themselves with cancer, failed. Finally, it is the universal experience of surgeons that the disease is not contracted by the treatment and care of cancer patients.

The conclusion may thus be drawn, that nothing in the incidence of cancer points to its infectious nature.

Microörganisms in Cancer.—With the advent of microbiology each new class of microörganisms in turn was isolated from cancer tissue, many were grown in pure culture, and some were claimed to reproduce the disease upon inoculation.

(*a*) *Bacteria.*—Rappin, Schill, Francke, Lampiasi, and others made unwarranted claims for the data regarding the bacteria isolated by them and they were soon forgotten. In 1887, Scheurlen obtained pure cultures of a bacillus from mammary cancer and with it claimed to have produced tumors of the breast in dogs. Baumgarten showed this bacterium to be the potato bacillus. In 1890 Koubassoff offered a complete claim of evidence for a thick motile bacillus from gastric cancer. In 1910 Doyen announced his *Micrococcus neoformans* as the cause and cure of cancer. It was soon shown that this microörganism had nothing to do with cancer, and the Societe de Chirurgie (1905) reported it to be valueless in the amelioration of the disease. These studies led to certain results of positive value. Shattuck and Ballance showed that non-ulcerated tumor-tissue could easily be kept sterile. Verneuil in necrotic foci and Zahn in some metastatic growths at autopsy found many bacteria. Richet found pyogenic bacteria common in cutaneous cancers. Maragliano often found staphylococci in the blood of patients with ulcerating tumors, even without fever, but never with non-ulcerating growths.

(*b*) *Coccidia*, differing in many details, were described by several observers.

Darier's psorosperm of Paget's disease secured much support from Wickham and the histological evidence alone sufficed to impress many with the belief that this structure was the true cause of this and other cancers. It was repudiated by its discoverer in 1904.

Thoma (1888) and Sjöbring (1890) described much the same intracellular and intranuclear structure as a parasitic coccidium.

Metchnikoff supported Sudakiewitsch's intracellular coccidium.

Adamkiewicz asserted that all cancer-cells are parasitic coccidia (*Coc. sarcolytum*) giving origin to a specific toxin (cancroin) and much this same view was held by L. Pfeiffer and J. Clarke.

(*c*) *Miscellaneous Protozoa.*—Other observers could not regard all the cancer-cells as alien parasites, but certain of the tumor-cells they identified as parasitic amebæ because of their bizarre forms and long pseudopodia which stretched between adjacent cells. These were the *Rhopalocephalus carcinomatosus* of Korotneff, and *Cancriameba macroglossia* of Eisen. L. Pfeiffer described and depicted intracellular structures which resembled the microsporidia of muscle-tissue.

Podwyssoski and Sawtchenko described as sporozoa a variety of free and encapsulated intracellular structures many of which resembled Sudakiewitsch's parasites. Ruffer and Walker improved the technical methods of demonstrating the cancer bodies and endeavored to distinguish between true and spurious parasites. Kahane thought he detected a minute protozoan in the circulating blood of cancer patients. In cancerous ascitic fluid Schaudinn observed a large ameboid cell which he named Leydenia gemmipara. Schüller traced the complete cycle of a minute intranuclear protozoön in cancer-cells which differed from nearly all other cancer parasites.

Bird's-eye Inclusion.—From the beginning of the search for the cancer parasite special interest always centered in a certain intracellular body called the "bird's-eye inclusion."

This body appeared in the cycle of many of the parasites described by various authors. It was first cautiously suggested by Foa as the probable cancer parasite. In 1902 Feinberg made a final effort to establish specific features in this body, double contour, metachromatism and nucleus surrounded by a clear zone, but these features were promptly and authoritatively discarded by Hertwig.

(*d*) *Mycetozoa.*—L. Pfeiffer early pointed out the resemblance of many cancer bodies to forms of mycetozoa, especially Plasmodiophora brassicæ. This organism was first described by Woronin as the cause of club root, a common disease of plants, and its complex cycle was worked out by Nawaschin. Some of its forms closely resemble the bird's-eye inclusion of cancer, while others are extremely minute and difficult of detection in the infected cells. Behla found the disease common in the gardens of his cancer houses in Luckau. Elaborate attempts to demonstrate that this or a similar organism is the cause of cancer have been made by Behla, Podwyssoski, Feinberg, Gaylord, and Robertson and Wade.

Several observers claimed to have secured cultures of these protozoa and to have reproduced tumors by inoculation of the cultures in animals. Sjöbring used a medium containing ascitic fluid, peptone, glucose and soap made from human fat, and claimed to have isolated his rhizopod from human tumors. Cultures produced tumor-like growths in mice. Yet the German pathologists denied that the growths were neoplasms and Israel asserted that the rhizopods were fat droplets. By the inoculation of material from club root Podwyssoski and Gaylord produced granulomatous swellings in animal tissues, the cells of which contained the englobed parasites, which closely resembled some of the intranuclear bodies seen in cancer. Yet v. Tubeuf and others have inoculated many animals with club root and failed to produce any lesions resembling neoplasms. According to v. Tubeuf the histology of club root is not that of a neoplasm, the tumor resulting from distension and degeneration of cells surrounded by an area of inflammatory overgrowth. The picture of infected cells in club root distended with enormous numbers of very definite parasites is wholly different from anything seen in cancer.

Smith has shown on an elaborate scale that *Bacillus tumefaciens*, isolated from crown gall, is capable of producing a variety of tissue overgrowths in plants which he regards as true tumors, both simple and teratomatous. Yet this observer fails to distinguish between chronic productive inflammation in plants and neoplasia, he does not consider that even in animals inflammatory hyperplasia may pass into neoplastic, while his infectious "embryomas" in plants cannot have any relation to the embryogenic disturbances known to give rise to teratomas in the animal body.

Schüller claims to have cultivated his protozoön and to have produced by it both carcinoma and sarcoma. Yet no one else has been able to find this organism in cancer and Schüller's technic fell under suspicion when Volcker pointed out that the very characteristic large forms of this protozoön exactly resemble cork cells.

(*e*) *Spirochetæ.*—In 1905 Borrel reported the occurrence of spirochetæ in two mouse tumors without attributing to them etiological significance. Wenyon has shown that mice are susceptible to blood infection by these organisms. Gaylord and Calkins, finding a single type of spirochetæ in ten mouse cancers and in 16 transplants therefrom suggested that the spirochetæ were the cause of the tumors. Yet Gaylord and Clowes succeeded in freeing their tumors from spirochetæ by treatment with KCN, and Tyzzer found many tumors in mice not infected with spirochetæ. In

thirty-five human tumors and twenty-five in the dog I found spiral organisms only on ulcerated surfaces or in necrotic areas. Similar results were obtained by Mulzer and by Lowenthal.

(*f*) *Blastomycetes.*—In 1890 Russell fully described certain small and large round bodies in cancer-cells which stained intensely with fuchsin and which he recognized as parasitic budding fungi or yeasts. Although these bodies had long before been noted by Fox, and Klein and Lubarsch soon showed that they were found in many normal and diseased tissues, the yeast theory of cancer was taken up systematically by San Felice and the Italian school. From 1895 up to the present time San Felice has devoted much labor to the support of this theory. He experimented first with a culture obtained from fruits, *Saccharomyces neoformans,* and one from the lymph-nodes of an ox dying with carcinoma of the liver; *Saccharomyces litogenes.* Later he obtained cultures from human tumors. With these cultures he produced infection of many animals, chiefly dogs.

With *Saccharomyces neoformans* he thought he produced a sarcoma in the breast of a bitch and in many other animals, but most of the lesions were clearly inflammatory. *Saccharomyces litogenes* produced very similar lesions.

Repeated passages increased the virulence of the strains and their neoplastic properties. Cultures from human tumors were non-pathogenic for animals. It was not possible to recover the organism from the tumors, a result which San Felice attributed to the death of the yeasts which then assumed the form of fuchsin bodies. In his latest studies San Felice combines the soluble toxines of yeasts with the living cultures, finding that the toxines rather than the bodies of the organism cause proliferation of cells. Nevertheless the lesions which he pictures seem to have the features of infectious granulomas and not those of tumors.

Many other observers claim to have isolated blastomyces from tumors and produced other tumors by inoculation, as Plimmer, Roncali, Corselli and Frisco, Curtis, Monsarrat, Leopold, Wlaeff, Klein, etc. Against their conclusions stand an equal number of very competent studies which show that blastomyces are rarely present in tumors and that they are incapable of producing neoplastic lesions. Foulerton and Richardson examined several hundred human tumors without securing a single yeast. Their rare presence in tumors is attributed by most bacteriologists to secondary infection, and the high proportion of successful cultures secured by many observers is clearly the result of air contamination. Meser found lycopodium seeds from the dressings deep within the tissue of carcinoma. The pathogenic action of a number of yeasts have been elaborately studied by many competent observers including Mafucci and Sirleo, Foulerton, Rabinowitsch, Petersen and Exner, and Nichols, none of whom found any indication that these organisms can produce tumors.

The various blastomycetes known to be pathogenic for man produce characteristic granulomas but not tumors. It is true that in certain chronic blastomycotic lesions, especially of the skin, considerable hyperplasia of epithelium resembling cancer has occasionally been seen, but there is no indication that this hyperplasia exceeds that observed with syphilis and tuberculosis. Genuine cancer sometimes follows such lesions and yet no one supposes that the tubercle bacillus is the cancer parasite. The identity of yeasts, dead or alive, with Russell's bodies has been subjected to careful criticism by many observers, especially by Sternberg and Nichols, who conclude that there is no adequate proof that blastomyces produce any considerable proportion of the fuchsin bodies.

Otto Schmidt claims to have isolated from human carcinoma and sarcoma

an organism which he calls *Mucor racemosus* and which he believes falls in the class of mycetozoa. With this organism he has produced ten sarcomas in rats and mice, some of which he has transplanted through several generations, the tumor strain finally reaching 100 per cent. of successful implantations. He is able to immunize rats against the organism and against its tumor-producing properties, and rats with tumors he is able to cure by inoculation with killed cultures of the mucor. Six out of 19 cancer cases at the Heidelberg Institute gave what he regards as anaphylactic reactions against the mucor. Baisch has succeeded in verifying some of Schmidt's results. On investigation it does not appear how often Schmidt secures cultures from human tumors nor with what precautions the successful cultures were obtained. The mucor cannot be identified in sections of the tumors. Some of the growing forms of the parasite Schuberg regards as fat droplets. From the experimental tumors the parasite is not recoverable. Ten tumors were produced, but hundreds of animals were used and it does not appear that the proportion of successful results greatly exceeds that of spontaneous tumors in rats subjected to other traumatic influences. The cure of the rat tumors is accomplished after very severe intoxication by the injected cultures and the death of many animals. Schmidt claims to have cured human cancer by his toxins but others have not succeeded. There seem to be no grounds for accepting the conclusion that human patients show anaphylaxis to the cultures of mucor. In fact Schmidt has not adduced satisfactory evidence that *Mucor racemosus* has anything to do with human cancer. What he seems to have accomplished is to add to the list of toxic agents that are known to excite hyperplastic inflammation which, especially in rats, may exhibit metaplastic changes and possibly pass over into tumors. He has not apparently controlled his work by equally energetic efforts to produce similar changes by other agents. Yet his observations seem to fall in line with those of other observers who by various means succeeded in causing notable hyperplasia and metaplasia of animal tissues, as Fischer with Sudan III, Jores with Scharlach R in paraffin, Stohr and Stoeber with naphthalamin, paratoluidin, and amidoazotoluol, and Stoeber and Wacker, with indol and skatol. With the expressed juice or the nucleoproteids of yeasts Galeotti and Pentimalli have also produced a considerable variety of tumor-like hyperplasia in dogs and rats, but they hesitate to assume that these processes are identical with progressive neoplasms. It is even more doubtful if the agents they used actually occur in spontaneous tumors.

The Experimental Study of Tumors.—The inoculability of carcinoma was once supposed to demonstrate its parasitic nature. Long after Peyrilhe's failure several experimenters claimed to have succeeded in transferring cancer to lower animals by intravenous inoculations of fresh emulsions (Langenbeck, Follin, Velpeau). These results were later met with many more negative reports by Virchow, Weigert and Billroth. The more recent claims of successful implantations of human cancer into lower animals by Boinet (1894) (epithelioma into dogs), Juergens, 1896 (melanoma into rabbits); Dagonet, 1904 (epithelioma into a rat); and Werner, 1907 (carcinoma into a dog) leave open the question how far human cancer may survive in these animals. Extensive melanosis of the organs as well as local tumors followed the inoculations of human melanoma by Goujon, Lang and Bosc, and Vedel, while Pfeiffer thought he was able to carry his melanoma into one of a second series of mice. Yet Fischer repeatedly failed to transfer melanoma to rats and Roux and Metchnikoff were unsuccessful with the chimpanzee. In none of the successful cases does it appear that the resulting process was anything more than a local or general reaction to the cells and pigment intro-

duced. While it is possible that the reactions observed in some of these animals must be classed with the tumor-like processes produced by chemical agents acting upon tissue cells there is no proof that the injected human cells multiplied during the considerable periods over which the animals were observed.

Firket, Boinet, Gaylord, Lewin, Bosc and Vedel, and others, claim to have produced cancerous nodules by inoculation into animals of various human cancers. While it is impossible to detect definite fallacies in all of these cases, especially in that of Dagonet, there are many difficulties in the way of their acceptance. A much greater number of negative results are recorded by many observers, as Shattuck and Ballance, Fischel, Sticker, Hemmeter, and many others. Herzog found that the nodules first forming invariably disappeared if the animal survived long enough and this has been the common experience of many pathologists working in this field. The experience of the last decade with transplantable tumors, showing how narrowly balanced is the nutrition of tumor-cells, renders it extremely unlikely that human tumor-cells can proliferate extensively in distantly related animals. The frequency with which spontaneous tumors occur in laboratory animals has been greatly underestimated by most observers, but has been clearly pointed out by Tyzzer.

The apparent impossibility of inoculating tumors from one lower animal to another of the same species long stood as evidence against their parasitic nature. Since the transfer of tumors among lower animals has become extensively practised it has become evident that this inoculability does not favor the parasitic theory but rather stands strongly against it, since it has been shown that the tumor-cells are transplanted and no evidence of a parasitic agent has been obtained. It is, of course, conceivable that a parasite is transferred with the cells and maintains their tendency to growth, but no evidence of such a parasite has thus far been secured, and there is no indication of the existence of any such form of parasitism anywhere in the animal or vegetable kingdom (Lubarsch).

Therefore the results of the study of transplantable tumors are everywhere regarded as a new and serious obstacle in the way of the parasitic theory.

The development of epithelioma following *x*-ray burns is a phenomenon which upon analysis seems to prove that this tumor develops entirely apart from any parasite and arises through slow disturbance of the nutrition and mechanical relations of the epithelial cells.

Clunet has succeeded in producing a malignant sarcoma in a rat by repeated exposures to *x*-ray and, in a case reported by Senger, round-cell sarcoma seems to have developed after a lupus cancer treated with *x*-rays.

Chemical agents of great variety have been employed by many observers to produce tumors and not without a certain success.

Emanating from a different point of view, but falling in the same general class, are the results of San Felice, Schmidt and Galeotti and Pentemalli, previously mentioned, who by means of extracts of yeasts seem to have succeeded in rare instances in producing genuine malignant tumors in lower animals. Since the great majority of such attempts are failures, the occasional success may be accepted without in any way involving the conclusion that such agents are commonly at work in producing spontaneous tumors in man or animals. They seem merely to illustrate the indirect action of irritants on predisposed tissues, which is a principle of tumor genesis long since established by clinical and pathological studies in man.

Likewise the striking observations of Rous that filtered extracts of a transplanted and very virulent sarcoma of chickens causes the growth of the

tumor in a considerable proportion of cases, is probably to be classed as an instance of chemical stimulation of cells.

This observation has the additional interest that the chemical derivatives of this tumor possess an unusual capacity to excite the neoplastic hyperplasia and recalls the well-known observations frequently made in man, that normal cells are drawn into the tumor process by the gradual diffusion of some influence from the tumor-cells. As an alternate hypothesis one may assume that an invisible microörganism passed through the filter, but here again the evidence of the existence of such a parasite is defective.

There are several other observations that chemical agents arising in the course of tumor growth possess a notable capacity to excite tumor-like growths of tissue cells and it seems probable that in some instances genuine neoplasms have been produced by such agents.

By repeated subcutaneous injections of extracts of human cancer filtered through porcelain Mayet claims to have produced cancerous lesions in white rats, and Francotte and DeRechter report similar results with cancer juice in white mice. Hemmeter by local injections of filtered extract of cancer of the stomach from the dog has produced cancerous-like proliferation in the walls of experimental gastric ulcers in the dog.

Theoretical Objections to the Parasitic Theory.—It is often assumed that the establishment of a parasitic cause of cancer is surrounded by no more difficulties than those which beset the search for the causes of syphilis or other infectious diseases. It should be pointed out, however, that there are many theoretical objections which would render unusually difficult the establishment of any cancer parasite even though supported by strong objective data.

The known infectious diseases display features of incidence, course, and anatomical character which sharply separate them from malignant tumors. The study of the age and sex incidence of cancer presents a body of data which reveals a fundamental difference in the etiology of cancer and all known infectious diseases. The distribution of cancer is as widespread as inflammation in general, indicating that blastomatosis is not a subdepartment of the reaction of tissues to injury, but a distinct and separate phenomenon in the life of the cell. Over against degeneration and inflammation stand regeneration and neoplasia. The anatomical and physiological characters of malignant tumors differ essentially from those of known infectious processes. The isolation of the cells of origin of tumors is wholly different from anything recognized in parasitic diseases. The abnormal size of nucleus and cell body revealing overnutrition is contrary to the rule in infectious processes. The types and degrees of metaplasia observed in tumors find no parallels in inflammation. The progressive growth of malignant tumors reaches a degree which constitutes it a different pathological entity from the regenerative process in the healing of wounds and the reaction to irritants. Parasitic diseases cause regressive processes in the infected tissues and general deterioration of the system by toxic agents, but tumors exert no deleterious action on the system or on the organ involved or even on the cells affected except through secondary agencies. The metastases of tumors reveal conditions wholly different from any phenomena observed with infectious diseases. There is no more impressive illustration of the difference between tumors and infectious granulomas, which they most nearly resemble, than the comparison of the fate of tumor-cell emboli and of emboli from a tuberculous focus. In the former case the tumor-cells grow where they lodge, receiving only nutriment from the blood of the part; in the latter case the embolic cells die and the transported bacilli excite an

inflammatory process in the adjacent tissues. Similarly, transplantable tumors survive in the progeny of the transferred cells.

It is conceivable that an invisible parasite lives with the tumor-cell stimulating its growth and nutrition but there is no evidence of any such form of parasitism anywhere in the animal kingdom. Parasites occur in mitotic cells, especially in club root, but this process is not a tumor (Tubeuf). Where parasitism is known it is at the expense, usually, of the life of the cells, while degenerative processes in tumors are secondary.

Weigert and Roux assume that the growth capacities of the cells are determined in the ovum and can never be increased except by fertilization, and Ribbert concludes that a tumor-producing parasite is therefore inconceivable. Yet it must be admitted that the growth of cells is greatly influenced by the environment and that peculiar external irritants of parasitic origin may greatly stimulate the nutrition and growth of cells. It has also been assumed that tumors result from release of the restraints of growth, but our knowledge of the nature of growth restraints seems hardly sufficient to warrant the conclusion that parasites may not be concerned in abolishing these restraints. Biology cannot argue the cancer parasite out of existence but it can demand objective data in its support.

The general facts of the genesis of tumors are strongly against the possibility of a parasitic origin.

Tumors arise in some instances from a single cell (teratoma testis), in most cases from a narrowly circumscribed group of cells, and grow chiefly or exclusively from their own resources. The gradual inclusion of neighboring cells in the process is as well explained by the diffusion of chemical or other influences as by the transfer of a parasite, while there is much evidence directly in favor of the former hypothesis. The embryonic nature and isolation of the cells of origin of a large proportion of tumors, as embodied in Cohnheim's theory, are incompatible with a parasitic origin of such tumors, and yet they possess all the qualities of malignant neoplasms which are not known to be derived from embryonic cells. The occurrence of highly malignant congenital tumors in several members of the same family, as glioma of retina, reveals an embryogenic and hereditary disturbance as the essential factor. Clinical experience strongly impresses the importance of chemical and mechanical irritants and various disturbances of nutrition as the exciting causes of tumors. Here stand the numerous list of occupational cancers, from paraffin, anilin, chimney-soot, the predisposing influence of arsenic (Dubreuilh, Hutchinson) and tobacco, *x*-ray cancers, the influence of chronic mechanical irritation, and severe trauma. Likewise clinical observation and anatomical study reveal the fact that cancers which are not of embryogenic origin do not arise except after long continuous previous change in the tissue. These changes do not favor the establishment of any known form of parasitism but rather suggest disturbances in the nutrition and function of the cells. Thus Billroth expressed the conviction that without previous changes in the originating tissue cancer does not exist, and his report of an epithelioma arising after many years over most of the area of an extensive scar from a burn, well illustrates the basis for his belief.

Few writers have ventured to suggest that benign tumors can be of parasitic origin, and yet occasionally tumors which are otherwise indistinguishable from benign growths, as adenoma of the thyroid and leiomyoma, may exhibit all the characters of malignancy.

The developmental history of many tumors exhibits the natural unfolding of embryonic potencies. However extensive may be the scope of metaplasia in tumors, it cannot cover the facts observed in the field of malignant tera-

tomas. The teratomas arising from sex cells yield many pure forms of benign and malignant tumors on the one hand and highly complex structures approaching a parasitic fetus. The metastatic cells from such tumors again go on to develop specific structures in lymph-nodes and distant organs. Thus in a metastasis of an ovarian teratoma Lubarsch observed brain tissue and ependyma in orderly arrangement. Metastases of many tumors are distinctly organoid in character maintaining polarity in arrangement and functionating as organs. If the above phenomena are of parasitic origin then, as Wilms points out, the whole history of embryonic development must be conceived as within the scope of parasitism. Hopeless dilemmas arise when one attempts to conceive of the necessary properties of the cancer parasite. It must pick out minute aberrant groups of embryonic cells in protected situations even in the fetus of a healthy mother. Misplaced and embryonal tissue invaded by metastases escapes infection by the parasite. Shaffer and Lubarsch have described misplaced islands of gastric mucosa in the esophagus invaded by epithelioma of the esophagus but showing no hyperplasia. Berent observed a misplaced adrenal rest in the kidney unaffected by a metastatic nodule from epithelioma of the jaw. With the most actively growing metastases adult normal tissues are not infected but as a rule behave passively. In chorioma the parasite invades the fetal but spares maternal tissues. In the metastases of melanoma the parasite produces extremely rapid proliferation of cells in one case, or it remains dormant for many years.

Contrary to all known forms of parasitism the cancer parasite stimulates growth and nutrition of cells and renders them viable after transplantation in the same or other animals. It stimulates the absorption of nitrogen by the host (Cramer) and fails, except through secondary influences, to exert any toxic or deleterious action on the body.

In view of the considerations thus briefly reviewed it is impossible to regard as a valid hypothesis the conception of a specific group of parasites living in symbiosis with the cancer-cell and stimulating its growth and nutrition. All the facts are reasonably explained by regarding the cancer parasite as the cancer-cell. The temporary popularity of the search for a specific parasite must be attributed to the undue influence of the germ theory of disease which can be effectually combated only by further knowledge of the biology of the cell.

The Scope of the Relation of Parasites to Cancer.—Although the conception of a specific cancer parasite living in symbiosis with the cell and stimulating its growth is without definite foundation and is incompatible with the nature of many tumors, there remains a certain field for parasites as etiological factors in tumors.

In the familiar coccidiosis of the rabbit's liver parasitic ova excite a tumor-like proliferation of the bile ducts. The process is strictly dependent upon the presence of the ova and regresses when these are removed and hence it is not a true tumor, but it has some of the qualities of a neoplasm and these are dependent on a parasitic irritant.

In Bilharzia infection cancer of the bladder follows in a certain proportion of cases. Here the disease is true cancer, it is less intimately connected with the presence of the parasite, but it is nevertheless rather obviously a sequel of the infection and reveals a peculiar capacity of this form of irritation to produce cancer.

Lowenstein has described papilloma of the bladder in rats infested with Trichodes. Primary carcinoma of the liver in cows suffering from Distomiasis has been referred to the irritation of this parasite (Haaland). In a pap-

illomatous gastric tumor of pigeons Wasielewski has found a species of Dispharagus. Brumpt describes an adenoma of the stomach in monkeys as referable to infection by Physaloptera. Febiger has fully demonstrated the relation of Spiroptera to a gastric carcinoma in rats. Askanazy attributes to a trematode, *Apistorchis felineus*, an etiological relation to certain hepatic carcinomas in man, and similar relations have been claimed for Distomum spatulatum and Japonicum by Katsurada and others.

Many observers have considered the possible relation of trichinosis to carcinoma and several have stated that carcinoma is peculiarly frequent in chronic trichinosis (Langenbeck, Babes). I rather frequently find trichinæ in cancerous tongues.

Borrel has observed several cases of sarcoma and adenocarcinoma of the rat in which a nematode worm was found in the center of the tumor. Regaud and Saul have reported similar cases and Bridrè found several sarcomas in rats growing about cysticerci. Borrel finds acari in the early spontaneous lesions of the lymphosarcoma of dogs. In 12 early epitheliomas of the face in man he found numerous acari inclosed in the tumor-cell nests. In the nipple of certain cases of Paget's disease and cancer of the breast he finds acari or another animal parasite, *Demodex folliculorum*. Borrel admits that these same parasites occur not infrequently in the healthy skin or nipple where they usually produce hypertrophy of the sebaceous glands. These ecto-parasites he regards merely as the carriers of the true cancer virus.

Saul has also drawn attention to the occurrence of worms in mouse tumors, and in two human ovarian tumors he found a parasitic mite, Tarsonemus. It has been suggested that the Tarsonemus gained access to the material after its removal from the body.

All of these observations indicate that animal parasites or their derivatives have a peculiar capacity to excite hyperplasia in the tissues they infect. Yet it has not been proven that they are present in any but superficial tumors, or that their presence signifies anything more than a secondary invasion. Nor is it known that the tumor-like processes in which they are usually found have any other significance than the hyperplasia excited by Sudan III which regresses upon the removal of the irritant. In lower animals especially, animal parasites of the skin are very common while cutaneous tumors are rare.

Certain manifestations of syphilis have a close though indirect relation to tumors. The lingual cancer following leukoplakia may be regarded as the result of the disturbed nutrition and relations of the epithelial cells long established in the disease and yet the frequency of this form of cancer reveals a certain unusual capacity of syphilis to excite neoplastic growth. Likewise the syphilitic sarcoma described by Hansemann shows this same peculiar influence exerted on mesoblastic cells, the full scope of which is possibly not yet recognized.

Tuberculosis in several of its phases has an indirect relation to certain tumors. In a small proportion of cases of lupus, epithelioma develops through long disturbance of the nutrition and relation of the epithelial cells of the affected area. That there is something specific in the tuberculous process is suggested by the greater frequency of epithelioma after lupus than with simple chronic eczema.

In some forms of tuberculous lymphadenitis, tumors of endothelial cells develop under conditions strongly suggesting that the neoplasm is a sequel of the tuberculous infection. Tuberculosis may cause a widespread hyperplasia of the lymphatic tissues of the body with miliary lymphomas in many organs. The frequent association of lymphatic leukemia with

tuberculosis has suggested to many that this disease, which has several characters of a neoplasm, may be dependent on tuberculous infection or intoxication. Hodgkin's granuloma which is either tuberculous or caused by a related organism, has been shown in several cases to pass over into a sarcomatous process.

Hence the sequels of both syphilis and tuberculosis have a definite relation to tumors, which reveals the microörganisms as indirect cancer parasites. In both cases the resulting tumor process seems not to be dependent on the presence of the parasite but to arise from the natural momentum of the disturbance originally excited by the parasite.

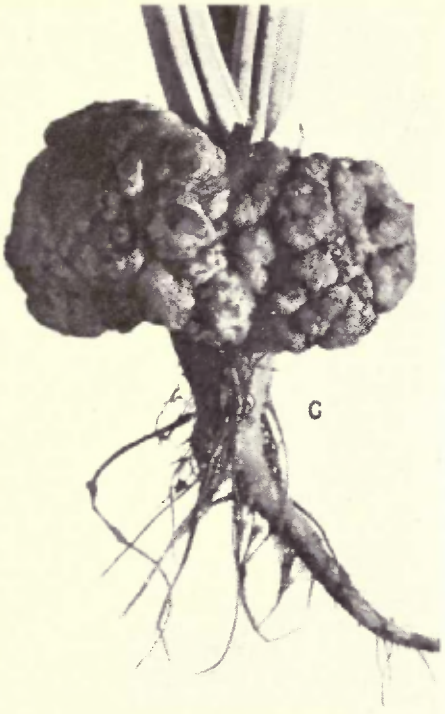

FIG. 11.—Growth resulting in 31 days from inoculation in sugar beet of *Bacillus tumefaciens* obtained from poplar gall. (*After Smith.*)

In the lower animals, especially in rats, the momentum of inflammatory processes which may lead to tumor growth seems distinctly less dependent on the presence of the parasites than in man.

In plants the observations on crown gall, especially those of Smith, point to the conclusion that in the vegetable kingdom progressive hyperplasias originally excited by parasites may be still less dependent upon their continued presence than in animals.

All these considerations encourage the search for new microörganisms which may have a special capacity to excite inflammatory processes which tend to go on to tumor growth, but they offer no support to the theory of a specific cancer parasite living in symbiosis with the cancer-cell and constantly stimulating its growth.

The results in this field show that parasites may be concerned only with

the inception of certain tumors but that their influence cannot explain the continued autonomous growth of malignant neoplasms, wherein lies the real mystery of the cancer process.

The study of the parasitic relations of cancer suggests the following classification of tumors with regard to their possible connection with a parasitic origin:

1. Tumors of embryonal origin and their derivatives to which Conheim's theory applies, and to which parasites have no relation whatever.

FIG. 12.—Centers of cell proliferation in daisy stem inoculated with *Bacillus tumefaciens*. (*After Smith.*)

2. Malignant tumors of exposed surfaces or internal organs with which parasites may figure as occasional indirect or direct exciting causes.

3. Sarcomas, especially those of lymphoid type, which are known to be the sequel of infectious diseases or on account of their imperfect neoplastic qualities may probably be regarded as more or less dependent upon the presence of parasites.

4. Tumors of lower animals in which the momentum of a parasitic process tends, more than in man, to assume autonomous qualities.