which entails this result is as follows: the vascular centers, vasomotor and sympathetic, along with the rest of the organism, become functionally depressed; as this causes relaxation of all arteries, including the cutaneous arterioles, the adventitious cell-aggregate receives an excess of blood (a process encouraged by the reflex influence of the sensory terminals it contains and which multiply with the tumor), and if the passive hyperæmia or congestion is sufficiently marked, it begins to grow, if already a defined tumor, or it assumes the characters of a tumor if merely a patch of abnormal cells.* In the case of moles, nævi, warts and other superficial conditions, traumatisms, *i.e.*, scratching, friction of clothing, blows, etc., are sufficient to initiate such a process in the same class of subjects, by greatly aggravating a local hyperæmia which might not otherwise have become sufficiently active to provoke development into a malignant tumor.*

The importance attached by many clinicians in recent years, as shown by the papers of Eve,[29] Wilson and Kalteyer,[30] Bloodgood,[31] Keen[32] and others, to the removal of warts, moles, pigmented nævi and kindred cutaneous excrescences lest they become malignant, harmonizes with these conclusions. Indeed, Eve found that out of 33 cases of melanosarcoma, 78 per cent. began in pigmented moles, while Wilson and Kalteyer found that out of 51 cases of cancer collected by them, 69 per cent. had their origin in a mole or nævus. Moreover, the well-known corresponding effects of prolonged irritation of limited areas by broken teeth, the pipe, scars, paraffin acne, lingual psoriasis, etc., sufficiently emphasize the pathogenic influence of localized processes. Bergmann,[33] in fact, asserts that carcinoma of the extremities does not occur without some cutaneous lesion, scar, fistula, ulcer, eczema, wart or mole as a precursor. Suggestive in this connection is the observation of Leo Loeb,[34] that in cattle the most frequent place for the occurrence of carcinoma is the inner canthus of the eye—a region greatly exposed to irritation and injury by twigs, strawtips and the like, while such animals are feeding. In an extensive study of cancer in the domestic animals, Sticker[35] found that in the horse the nose was commonly diseased, an organ considerably exposed to scratches and other traumatisms in the manger.

This applies likewise, in a certain sense, to cancer of the stomach, intestines, rectum, kidneys, bladder, gall-bladder and uterus. All these organs are exposed to the chemical and physical action of any abnormal constituent present in the substances passed through them—products of imperfect digestion in the alimentary canal, toxic wastes in the hepatic and urinary systems and in the uterine discharges, etc. Maniscalco,[36] by repeated chemical and mechanical irritation of the exposed gastric mucosa

* *Author's conclusion.*

[29] Eve: Practitioner, Feb., 1903.
[30] Wilson and Kalteyer: Amer. Jour. Med. Sci., Nov., 1903.
[31] Bloodgood: "Progressive Medicine," p. 204, Dec., 1903.
[32] Keen: Jour. Amer. Med. Assoc., July 9, 1904.
[33] Bergmann: Berl. klin. Woch., Bd. xlii, S. 932, 1905.
[34] Leo Loeb: Medicine, Apr., 1900.
[35] Sticker: Arch. f. klin. Chir., Bd. lxv, S. 1023, 1902.
[36] Maniscalco: Riforma medica, vol. xxi, p. 340, 1905.

of dogs, caused growths which presented all the features of cancer. Bazin observed, as stated, that cancer of the bladder and rectum *followed* gout; the prolonged excretion of poisonous waste-products obviously stands here as local irritant. This affords also an example of the manner in which chemical substances in the blood, secretions and excretions, can predispose a restricted territory of tissue-cells to cancer, by provoking therein the proliferation of new cells, atypical in the sense that, as inflammatory products, they are adventitious, and therefore, like warts, moles, and the like, menacing excrescences.

The functional relationship between the abnormal cell-aggregates and the nervous system is readily demonstrable even in such apparently functionless structures as a mole, a nævus, and the like, so prone, as stated above, to become malignant. Wilfred S. Fox,[37] in an exhaustive paper, remarks that "this connection between moles and the cutaneous nerve-supply is not surprising when one considers the intimate developmental relation between the skin and the nervous system." Foldau[38] traced nerve-fibers in these structures, while Bergmann[39] states that multiple pigmented nævi also contain nerve terminals. That they persist in cancerous neoplasms is shown by the fact that H. H. Young,[40] using Ehrlich's methylene-blue method in ten freshly removed carcinomata and sarcomata, found distinct axis-cylinders sometimes in considerable numbers, in no less than five growths, *i.e.*, cancers of the breast, cervix and tibia.

As to the rôle of the vasomotor nerves—which govern nutrition—G. Lenthal Cheatle[41] pointed out that a proportion of cases of cancer showed a "marked relationship between the spread of the primary focus and the distribution of nerves and *trophic* areas" and adduced a large number of cases, convincingly illustrating the close relationship between the initial lesion of cancer (frequently a mole) and points at which nerves become cutaneous, including the maximum pain points of Head.[42] Although most of the cases related are not—in the light of my views—truly cancerous (being instances of rodent ulcer due to *deficient* nutrition of the cutaneous elements, and not of *growths* due to *over*nutrition of these elements) the fact remains that they clearly sustain Cheatle's opinion that trophic nerves are concerned in the morbid process.

The influence of senility, the uric acid diathesis and other predisposing conditions have already been reviewed. That this should entail depression of the vascular nerve-centers, and, therefore, general vasodilation and passive congestion of any moles or other excrescences present, is self-evident. The effects of injury on these small growths are now thoroughly recognized. Thus W. W. Keen[43] writes that "all such growths are exposed to traumatism, such as blows, friction of the clothing, scratching on account of the itching, or in many cases on account of the presence of a little scab—and who can and does resist the temptation to scratch off these scabs?" . . . . "In consequence of such injury or repeated and long-continued irritation—or in other cases without any assignable cause—they begin to increase in size. This sudden activity and increase in size usually does not occur for months or more likely years; it may be thirty or fifty years, or even more, after the mole or wart was first noticed. The moment they begin to increase in size, they are, I believe, almost invariably malignant growths."

All this (apart from the traumatisms, which probably act as ex-

[37] Wilfred S. Fox: Brit. Jour. of Dermat., Jan., 1906.
[38] Foldau: Cited by Cheatle: Brit. Med. Jour., Apr. 18, 1903.
[39] Bergmann: *Loc. cit.*
[40] H. H. Young: Jour. of Exper. Med., Jan., 1897.
[41] G. Lenthal Cheatle: Brit. Med. Jour., Apr. 18 and Dec. 12, 1903.
[42] Head: Brain, vol. xvi, p. 1, 1893; vol. xvii, p. 339, 1894.
[43] W. W. Keen: *Loc. cit.*

citing causes of cancer of the breast and bones) is as applicable to the pathogenesis of internal cancers, the passive vasomotor hyperæmia being sufficient here to start the process of growth in a restricted area, the uterine os, for instance, which has become the seat of a local predisposing disorder, a chronic catarrhal process, cicatricial tissue incident upon parturition, etc., any condition, in fact, involving localized cell proliferation.

At first, the process of growth is localized, in the sense that the body at large does not participate in it. When, however, the tumor has reached a certain size, its presence becomes a menace. Its structure differing from that of normal tissues in that the channels for the elimination of broken-down cells, waste-products, etc., are either absent or very imperfect, it becomes, in respect to the body at large, a source of auto-intoxication. This evokes a general febrile reaction similar, in a measure, to that provoked by a subcutaneous abscess. The adrenal system being stimulated, the blood soon becomes supplied with an excess of auto-antitoxin, the constituents of which permeate the growth as they do all other organs during fever.*

The development of the tumor is thus intimately merged with the immunizing process.* There is excessive oxygenization, owing to the overproduction of adrenoxidase and, therefore, of trypsin and nucleo-proteid.* There is also an abundant leucocytosis, the cells serving not only to supply the fluids of the growth, the trypsin and the nucleo-proteid found in it, but also to insure active phagocytosis.*

The general reaction is sufficient in some cases to provoke fever—which occurs only when the adrenal system is violently stimulated. Fretel[44] observed a rise of temperature in the absence of any complication, especially in cancers of rapid evolution. Freudweiler,[45] at the instigation of Eichhorst, studied the clinical histories of 475 cases of carcinoma, and found that the temperature exceeded 38° C. (100° F.) in no less than 117, although all cases in which some complication existed were excluded. Even the central phenomena of a febrile process are present. De Buck and Van der Linden[46] found the tendon reflex invariably exaggerated, while Klippel[47] noted a marked hyperexcitability of the muscles, contraction being produced very readily by percussion.

The three constituents of the "functional triad" which constitute the active agencies of the febrile process, *i.e.*, the auto-antitoxin, have been found in the growths themselves, thus proving that they take part in this process.

The presence of *adrenoxidase* in these growths is shown by the characteristic tests. Thus, Hugounenq and Paviot,[48] in soft malignant

* *Author's conclusion.*
[44] Fretel: Thèse de Paris, 1899.
[45] Freudweiler: Deut. Arch. f. klin. Med., Bd. lxiv, S. 544, 1899.
[46] De Buck and Van der Linden: Presse méd., vol. x, p. 10, 1903.
[47] Klippel: Arch. gén. de méd., vol. clxxxiii, p. 33, 1899.
[48] Hugounenq and Paviot: Lyon médical, vol. lxxxii, p. 1, 1896.

tumors, not only obtained the typical guaiac reaction, but also the intense violet of the paraphenylene-diamine test. Moreover, boiling of the cancer fragment destroyed this specific property, which was not marked where the process of growth was most active. They characterize as "oxidizing diastase" the "soluble ferment" to which they ascribe these results, and compare the latter to those of Bertrand and Bourquelot, referred to in the thirteenth chapter of this work. The presence of *trypsin* in cancerous growths is no less evident. Stewart[49] found a high percentage of trypsin in secondary growth of the liver and lung in a case of pancreatic cancer. This suggests direct metastasis, but we have seen that trypsin is present in all cells, as shown by the researches of Hedin, Cohnheim, Opie and others. Blumenthal,[50] moreover, found a corresponding enzyme in cancer cells, not specific to cancer cells alone, but capable of attacking all tissues. The third constituent, the *nucleo-proteid*, is likewise present in all tissues, as already shown. That leucocytes (which secrete this substance in the form of granules) are present in large numbers, is well known. Thus, Herbert Snow[51] pointed out twelve years ago that every variety of malignant growth exhibits from its earliest initiation, an extremely copious immigration of leucocytes, which steadily increases. Bushnell[52] found that this sometimes reached as high as 32,580. Snow noted, however, that this *leucocytosis* was restricted to the normal tissues immediately bordering the cancerous parenchyma. This has been confirmed by many observers, and recently by Farmer, Moore and Walker.[53] Even the specific (oxyphile) granules themselves have been found in the tumors by Ehrlich, Löwit and Przewoski,[54] although these investigators were not aware of their functions. The granules took acid aniline dyes readily, did not become black under osmic acid, etc., the characteristic tests. They were of course observed in *extra* corpus specimens, and therefore under abnormal conditions. During life, however, they dissolve in the blood, and, with the adrenoxidase and trypsin, form the "digestive triad" or auto-antitoxin, distributed throughout the growth itself.

The tumor is supplied with the elements for its development, *i.e.*, the nucleo-proteids out of which its tissues are nourished by the leucocytes.* These cells, as previously shown, ingest food-products and enterokinase—which contains trypsin—in the intestinal canal and convert them into granulations which they carry to the lymphatic spaces and deal out to the tissue-cells.* The chromatin of the latter, which undergoes atypical mitosis and other transformations, was also shown to be derived from the leucocytic granulations.*

Bashford,[55] referring to various hypotheses upon the mode of origin and nature of cancer, states that "they fail to show how the actual cell multiplication is maintained." In truth, it is upon this point that they have all collapsed.

* *Author's conclusion.*
[49] Cited by Morris: Review of Reviews, Dec. 25, 1903.
[50] Cited by Von Leyden: "Ueber die parasitäre Theorie in der Ætiologie der Krebs.," Berlin, 1805.
[51] Herbert Snow: Brit. Med. Jour., Sept. 22, 1894.
[52] Bushnell: *Ibid.*, Sept. 12, 1903.
[53] Farmer, Moore and Walker: *Ibid.*, Aug. 12, 1905.
[54] Przewoski: Centralbl. f. allg. Pathol. u. path. Anat., Mar. 15, 1896.
[55] Bashford: Lancet, Apr. 1, 1905.

French investigators long ago observed that the leucocytes exerted a fructifying influence upon cancer cells, causing them to multiply.[56] The manner in which they do so, however, has never been explained. The direct participation of the leucocytes outlined in the text affords this explanation. Indeed, as I have pointed out, these cells are the actual builders of living tissue. This implies that the mitotic figures observed in cancerous masses, and now regarded as reproductive cells, are really nothing but those common to ordinary cells, including leucocytes. Bashford wrote recently:[57] "During the past year a paper has been communicated to the Royal Society, showing that the nuclear figures in cancer cells, believed to indicate the occurrence of a true 'reducing division,' are in reality of the ordinary type. Dr. Murray and myself have invariably denied that the presence of cell-divisions resembling tnose of reproductive tissue were a means of distinguishing benign from malignant new growths."

This accounts for another paradoxical fact emphasized by the Royal Cancer Research Fund investigators, namely, that, as stated by Bashford,[58] "the influence of age is active in relation to the *origin* of cancerous growth, and not in relation to its *continuation;* for cancer can be propagated almost better in young than in old animals." As I have stated, age stands merely as a predisposing factor, while the general vasodilation which it engenders and the febrile process, by flooding the tumor with nutritional elements, are the causes underlying its growth. As young animals are better able to promote a vigorous febrile reaction than old ones, the process of growth is all the more active.

Again, "malignancy," if these processes actually prevail, should merely mean excessive tissue-growth. The labors of the Royal Cancer Research investigators also sustain this conclusion. Bashford[59] remarks in this connection: "What is understood by the malignancy of a tumor is but a manifestation of the power of growth: a conclusion to which Ehrlich and Apolant have recently given confirmation." The Cancer Research Commission also confirmed Jensen's conclusion that the growth of artificially propagated cancer was due to the continued proliferation of the parenchyma cells—a logical outcome, I may add, with the leucocytes as the normal purveyors of nutriment to the normal parenchyma.

There are, of course, several varieties of carcinoma: (1) *epithelioma,* consisting of surface epithelium, which includes two kinds: the *squamous* of the skin and mucous membrane of the lips, œsophagus, and cervix uteri, etc.; and the *cylindrical* or columnar of the gastric, intestinal and uterine mucous membranes; (2) the *granular,* consisting of acini or alveoli in layers —and which may become fibrous, the scirrhous form—and growing mainly in the pylorus, mammary gland, pancreas, kidneys, ovaries and testicles; (3) *colloid* or gelatinous, consisting of transparent, jelly-like masses, containing degenerated tissues and epithelial cells, and met with in the ovaries, stomach, intestine, peritoneum, and mammary gland; and (4) *deciduoma*

[56] Warren: "Surgical Pathology and Therap.," vol. ii, p. 643, 1895.
[57] Bashford: Brit. Med. Jour., July 26, 1906.
[58] Bashford: *Ibid.*, Dec. 9, 1905.
[59] Bashford: *Ibid.*

malignum of the placenta, consisting of fœtal epithelial cells (syncytium) and of different cells of the chorion villi.

Several varieties of sarcoma are also described: (1) *spindle-celled sarcoma,* which occurs in the connective tissue of bones, tendons, fasciæ, and occasionally in the soft tissues; (2) *round-celled sarcoma,* often permeated with large blood-vessels, and more malignant than the former, is itself divided into two varieties: *lymphosarcoma,* which occurs in the lymphatic glands and the lymphadenoid tissues of mucous membranes, and *alveolar sarcoma,* which contains also spindle-cells, acini filled with large, round cells and fibrous tissue, and is notable because it commonly develops from cutaneous moles, nævi and warts, and from lymphatic glands and serous membranes; (3) *angiosarcoma* (a very malignant growth), which starts in the external coat or adventitia of blood-vessels, is usually very vascular—thus exposing them to rupture and provoking hæmorrhage—likewise grows, as a rule, on the skin and particularly from pigmented warts and moles, and also in the eye and the pia-mater; (4) *giant-celled sarcoma,* a relatively benign growth, which usually occurs in bone or bone-marrow (hence often called osteo- or myelo-sarcoma), the large multinuclear cells of which resemble the myelo-plaques of bone.

The difference between all these varieties depends upon the histological composition of the structures which form the tumor. At first, all the tissues composing the affected area are involved in the hypertrophic process; eventually, however, the epithelium in carcinoma or the connective tissue in sarcoma grows with greater rapidity than all the other local structures and soon constitutes the bulk of the tumor. The development of sarcoma coincides, however, with the maximum energy developed, *i.e.,* with the most active local accumulation of nutrient leucocytes and of the energizing agents, adrenoxidase and nuclein, which this phenomenon entails.*

All the various varieties of cancer enumerated are ascribable to the same cause: a primary focus of proliferation-cells due to local (active or passive) irritation, which eventually provokes marked local congestion and excessive nutrition.* Important in this connection, however, is the fact that this local

* *Author's conclusion.*

hyperæmia and accumulation of all the constituents of the blood which usually provoke inflammation do not initiate the latter in cancerous growths.* The local congestion, leucocytosis, etc., are associated with a process distinct from that of inflammation though linked with it, *i.e.*, the process of tissue repair.* Were it otherwise, the tumor would not grow; it would be destroyed, and as will be shown, it is by provoking active inflammation in the growth itself that cancer can be mastered.*

Many investigators, including Israel,[60] now ascribe to relative overactivity, the proliferation of epithelial cells over all others, with persistent excitation as a primary cause. Even in the giant-celled sarcoma, though situated in osseous tissues, this exciting cause prevails. Ziegler maintains, writes Stengel,[61] referring to this variety of growth, "that the presence of giant-cells does not form an essential characteristic of a peculiar type of tumor, but that it is accidental, resulting from *continued irritation*." The result of this irritation also manifests itself by overnutrition in sarcoma. Thus, H. W. Cattell[62] states that "it is at times impossible from microscopical study alone to tell a sarcoma from *granulating tissue*."

It is now generally conceded that at first all the elements of the tissue involved are more or less urged to grow as shown by Schuchardt.[63] In the early stage of cutaneous epithelioma, he observed that "not merely the epithelium, but all the tissues of the skin, the connective tissue as well, show hypertrophic changes," though "later, the overgrowth of epithelial cells outruns and overshadows that of the other tissues."

That sarcoma, in which the connective tissue predominates, is but an advanced stage of the carcinomatous stage, was recently observed by Apolant and Ehrlich,[64] in the course of inoculation experiments in mice. The carcinomatous type was traced up to the sixth generation. By the tenth a change had occurred: the tumor was a mixed one, a sarcomatous stroma predominating. By the fourteenth, no carcinomatous tissue remained. They refer to a similar transition in man, observed by Schmorl, a case of epithelioma of the thyroid. After removal, the tumor, which recurred locally, was a mixed carcinoma and sarcoma. A second removal being followed by death from metastasis, all the growths examined were found to be pure spindle-celled sarcomata. Hansemann[65] has encountered carcinomata with sarcomatous stroma, and refers to twenty cases in literature. Apolant and Ehrlich did not always obtain such prompt transitions, however. In some instances the mixed growth was only reached in the sixty-eighth generation; then followed a violent reaction, during which the tumor became a pure sarcoma. So great was this "energy of growth" that in the course of a few weeks, in some instances, the tumor was larger than the mouse itself. They state that at the present time no explanation is available for this phenomenon, though they suggest that the development may be due "to chemical changes in the carcinoma cells and gradual stimulation of the connective tissue cells." What better and more solidly grounded explanation can there be vouchsafed than one of which *all* the elements of growth are actually present in the tumor, as we have seen, and which *alone* can account for the violent "energy of growth" to which they refer? We are thus brought to consider overnutrition as the underlying cause of *all* types of malignant growths.

* *Author's conclusion.*

[60] Israel: Archiv f. klin. Chir., Bd. lxvii, S. 446, 1902.

[61] Stengel: "T. B. of Pathol.," third edition, p. 154, 1900.

[62] H. W. Cattell: Sajous's "Analyt. Cyclo. of Pract. Med.," Art. "Tumors," vol. vi, 1901.

[63] Schuchardt: Archiv f. klin. Chir., Bd. xliii, S. 255, 1892.

[64] Apolant and Ehrlich: Berl. klin. Wochen., Bd. xliii, S. 871, 1906.

[65] Hansemann: Zeit. f. Krebsforschung, Bd. i, S. 183, 1904.

All malignant tumors being the outcome of a localized overdevelopment of cells initiated by irritation of the area involved, any agent capable of provoking the appropriate type of irritation can cause a cancer. As various parasites, including bacteria, have, in the hands of the upholders of the parasitic theory, provoked the formation, local and remote, of cancerous growths, there may be classes among these appropriate irritants.* Moreover, as the growths developed through inoculations and implantations present the morphological organization of sporadic cancers, those provoked by the upholders of parasitic theories are true cancers.* It cannot be said, however, that cancer is a parasitic disease, since all malignant growths can be caused by various factors, intrinsic and extrinsic, which irritate the tissues, irrespective of any parasite.*

The multiplicity of these factors also accounts for the epidemics of cancer, its repeated occurrence in certain houses or districts, and for the cases of direct contamination on record, since the presence of any of the appropriate irritants in these houses or districts or on the contaminating surface, whether this be normal or the seat of malignant growth (both fragments and fluids therefrom being effective inoculative agents), is sufficient to start a malignant process in predisposed tissues.* A tissue being predisposed to malignancy when it is the seat of adventitious cells in an aged or debilitated subject, an ulcerated surface, however small, on the lips, tongue, œsophagus, uterus, etc., may become a vulnerable spot if it happens to become inoculated when any one of the cancerogenic factors happens to become implanted therein.*

Merged in with the tissues of the tumor and imprisoned among them are cells which have been taken by many investigators as the specific cause of cancer. Cornil,[66] Fabre Domergue and others have shown that the many cellular and nuclear elements present could readily be taken for parasites. The nuclei, which are rich in chromatin, soon become fimbriated, knobbed, sometimes œdematous, and finally achromatic, assuming at the same time most varied shapes and appearances.

* *Author's conclusion.*

[66] Cornil: Boston Med. and Surg. Jour., Apr. 19, 1894.

Councilman[67] also found that parasites to which specific properties had been attributed, were present in many morbid processes other than cancer. In accord with this observation, Borrel[68] pointed out that the sporozoa associated with tissue-proliferation in sheep-rot, variola, bovine pest and other diseases, corresponded with the detritus of worn-out leucocytes. Borrmann[69] recently showed, moreover, that none of the so-called parasites are found in very small, young cancers, thus eliminating them as a cause. Transplantation experiments are as conclusive. Jensen,[70] for instance, made transplantations in 844 mice and obtained successful results in about 50 per cent. Although cell inclusions were undoubtedly present and the tumors grew until the mice died of cachexia, he never observed parasites, and experimental inoculation invariably gave negative results. This has been confirmed, according to Bashford,[71] in the Royal Research laboratories, where at least 50,000 transplantation experiments were performed. Referring to researches conducted under the same auspices, Sir William Church[72] states that "large numbers of healthy mice have been kept for long periods in the same cages with mice suffering from both sporadic and inoculated tumors," and that "in no single instance did the malignant growth occur in an inoculated mouse." As emphasized by Leo Loeb,[73] though he had carried on highly successful experimental inoculations, inoculability does not mean infectivity. On the whole, as stated by Senn[74] at the recent Lisbon Congress, in reference to the specificity of microbes and other parasites in cancer: "Searching criticisms from different reliable sources have disarmed all such claims."

Nevertheless, the fact remains that many investigators, beginning with Morau, in 1885, *i.e.*, Sanfelice,[75] Roswell Park,[76] Gaylord,[77] Doyen,[78] Sticker,[79] Vischer,[80] Schmidt,[81] and many others, have obtained by inoculation growths resembling cancers to such a degree that microscopical examination was necessary to determine their identity. In the light of my views, as defined above, the reports of the opponents of the parasitic theory indicate that these growths were true cancers. "By the investigators themselves," writes Lazarus-Barlow,[82] "they have been regarded as 'epithelial,' 'malignant,' etc., but by opponents of the parasitic theory they are confidently asserted to be 'infective granulomata,' that is, inflammatory." Cornil, Cazin[83] and others also concluded that the tumors produced by parasites were of this nature. Even the cancers which Doyen obtained by inoculations with a supposed specific microbe, were found by Weinberg,[84] of the Pasteur Institute, after a careful examination, and also by Cornil, to be an inflammatory "proliferation of tissue." This conclusion indicates the cancerous nature of the growth, since the main landmarks upon which it could be based were the intense hyperæmia, the equally marked leucocytosis and the granulation tissue, all of

[67] Cited by Warren: *Loc. cit.*
[68] Borrel: Ann. de l'Inst. Pasteur, vol. xvii, p. 81, 1903.
[69] Borrmann: Münch. med. Woch., Bd. lii, S. 2028, 1905.
[70] Jensen: Hospitalstidende, vol. xi, pp. 549, 581, 1903.
[71] Bashford: Lancet, Apr. 1, 1905.
[72] Sir William Church: *Ibid.*, July 8, 1905.
[73] Leo Loeb: Jour. of Med. Research, vol. iii, p. 44, 1902; vol. v., p. 407, 1903.
[74] Senn: Jour. Amer. Med. Assoc., Apr. 28, 1906.
[75] Sanfelice: Annales de micrographie, 1894; Riforma medica, vol. xx, p. 981, 1904.
[76] Roswell Park: Med. Record, May 18, 1901.
[77] Gaylord: Trans. Med. Soc. of State of New York, Jan., 1899.
[78] Doyen: Brit. Med. Jour., Dec. 17, 1904.
[79] Sticker: Zeit. f. Krebsforschung, Bd. i, S. 413, 1904.
[80] Vischer: Bruns' Beitr. z. klin. Chir., Bd. xlii, S. 617, 1904.
[81] Schmidt: Münch. med. Woch., Bd. liii, S. 162, 1906.
[82] Lazarus-Barlow: "Manual of Gen. Pathol.," second edition, p. 504, 1904.
[83] Cazin: Revue des mal. cancéreuses, Oct. 20, 1895.
[84] Weinberg: Cited by R. S. Williams: Lancet, Apr. 8, 1905.

which, however, as previously stated, indicate an entirely different process, *i.e.*, excessive nutrition through the accumulation of blood and cells. Indeed, as stated by Councilman,[85] the characteristic of cancerous growths is that they are capable of attracting to themselves a supply of nourishment at the expense of the surrounding tissue, and necessarily, I may add, of the body at large. This is an attribute of all cancerous growths, whether sporadic or due to transplantation or inoculation.

This does not alter the fact, however, that as Orth[86] declared recently, "no one up to the present time has produced proof that carcinoma is of parasitic origin." All that can be said is that certain parasites can be included among the many factors of divers kinds that are capable of irritating the cellular elements which act as foci for the development of malignant growths. This accounts for an important corroborative fact adduced by the supporters of the parasitic doctrine, viz., that it clings to districts, buildings, or groups of buildings, that it may occur epidemically, as observed by Hvoslef[87] (all the cases being in aged subjects) and others, and that it has, though rarely, been communicated. With various exogenous and endogenous agents as pathogenic elements, quarters inhabited by cancerous subjects may readily become intermediary. This applies as well to direct contamination through contact with a malignant growth, since, as shown later, vestiges of such growths, or even their juices after filtration, can start a malignant process in an ulcerated mucous membrane. As this implicates the tongue, lips, œsophagus, uterus, etc., while an area of ulceration may be extremely small and still constitute a vulnerable spot, it is probable that more cancers are thus communicated than is now realized, irrespective of any specific parasite as cause.

Cancer cells, when placed in appropriate surroundings, retain their vitality several days, and when transplanted, continue to divide and multiply, preserving the characters of the original tumor. This accounts for the fact that malignant tumors can develop in regions remote from the original growths. The predilection of the lymphatic glands to metastasis, however, is due to the relative viability of these cells in lymph as compared to blood:* While the blood is destructive to cancer-cells, especially when its temperature (*i.e.*, its proteolytic activity*) is above normal, the lymph into which the cells pass on leaving the cancerous mass is not. This is mainly because (1) its temperature is lower than that of the blood, (2) its proteolytic activity is relatively slight and (3) its circulation is extremely slow (4 mm. per second). The cancer-cells being comparatively immune in lymph, they readily reach the lymph-glands which occur in the path of the lymph-streams and tributaries emanating from the main tumor.* As all tissues are permeated by lymphatic vessels, these afford ready channels for cancer-cells

* *Author's conclusion.*
[85] Councilman: Boston Med. and Surg. Jour., Sept. 14, 1899.
[86] Orth: Berl. klin. Woch., Bd. xlii, S. 281, 326, 1905.
[87] Hvoslef: Tidsskrift f. d. Norske Laegeforening, No. 17, 1903.

to every part of the body, a fact which accounts for the frequent occurrence of metastatic growths in regions remote from the original cancerous mass, and in all kinds of tissues. This is facilitated, moreover, by the fact that the cancerous fluids can also provoke the transformation of an aggregate of benign adventitious cells, the edges of an ulcer, etc., into a malignant growth and likewise cause the development of the latter when injected into the tissues.

Not every accessory growth should be regarded as metastatic, however, since cancers of a similar kind and even of different kinds have been known to develop in the same subject simultaneously.

Bashford[88] states that when cancer is successfully inoculated from one animal to another, "a few parenchyma cells retain their vitality and continue to divide and multiply, giving rise to large tumors at the site of inoculation;" the new stroma formed "assumes the distinctive features of the original stroma," the new tumor, therefore, being "exactly like the original one." Indeed, as emphasized by Albrecht,[89] metastatic growths in human cancer cases may even functionate, as do the organs from which they are derived.

The viability of detached tissues accounts for the resumption of their functions. Thus, Ljunggren[90] found that when carefully sterilized, bits of human skin could be preserved in sterile human ascitic fluids for months, and that the cutaneous cells retained their vitality. Transplanted pieces which had been in this fluid one month, subsequently showed marked proliferation of epithelial cells and many nuclear figures. The transplanted cells also penetrated into the granulation tissue beneath, as in beginning carcinoma. Jensen[91] observed a similar resistance in cancer cells, some living twelve days, isolated, at the room temperature. In the blood, however, matters were different: he found that at the temperature of the body they perished in twenty-four hours, and that at temperature *above* the normal they rapidly lost their vitality. Metastasis, therefore, can occur only under certain conditions, for it is only *when* or *where* the temperature is normal or below normal, that detached cancer cells can safely run the gauntlet of the blood's destructive action and reach a spot where they may, as it were, take root and grow. Indeed, as stated by Bashford,[92] the transmission of cancer differs from all known processes of infection: "the tissues of the new hosts do not acquire any cancerous properties; they merely react to the presence of cancer cells and supply them with nourishment." As explained in the text, a field where detached cancer cells are not endangered is unfortunately available as soon as they leave the tumor, viz., the lymphatic vessels themselves, the normal channels for all detritus, and which serve also for their general distribution, as stated below.

Even apart from the direct development of a tumor by transplantation thus provoked, a lesion anywhere, and characterized by an agglomeration of adventitious cells, may become the starting point of malig-

[88] Bashford: Brit. Med. Jour., Dec. 9, 1905.
[89] Albrecht: Münch. med. Woch., Bd. xlix, S. 1135, 1902.
[90] Ljunggren: Cited by Hektoen: "Progressive Medicine," p. 236, Mar., 1899.
[91] Jensen: Centralbl. f. Bakt., Bd. xxxiv, S. 122, 1903.
[92] Bashford: Brit. Med. Jour., Dec. 9, 1905.

nant growth when these cancerous vestiges are available. Thus Hemmeter[93] obtained gastric carcinoma in dogs affected with experimental peptic ulcer, by inoculating the animals with particles of canine adenocarcinoma. More striking, however, is the fact that he obtained similar results by injecting a sterile and cell-free filtrate of a similar growth. As Mayet[94] also obtained a splenic sarcoma by injections of a filtrate of a uterine myoma—a frequent precursor of cancer—it is evident that a fluid derived from the cancerous mass, and not necessarily cancer tissue, can start the malignant process. The ease with which the poison may be distributed being thus greatly increased, almost any preëxisting lesion in any part of the body is exposed to contamination, and may thus become the seat of cancer as was the case in Hemmeter's animals.

The *cancerous cachexia* is due to hæmolysis, the result, in turn, of the excessive proteolytic activity of the blood.* Both the red corpuscles and the hæmoglobin are actively destroyed, this morbid process beginning soon after the cancer begins to grow. The presence in the blood of an excess of adrenoxidase—and therefore of auto-antitoxin, to which this morbid process is due—provokes likewise an exaggerated vasotonus by stimulating unduly and directly the muscular coat of all arteries.* As a result of the vasoconstriction thus produced, the blood-serum is forced into the capillary system and lymphatics, causing various manifestations of œdema, anasarca, hydrothorax, puffiness, etc.* After death the caliber of the vessels is found considerably reduced, owing to the prolonged constriction to which they are subjected during life.* This also predisposes the patient to congestive disorders; hence the pulmonary congestion, the neuritis, phlebitis and kindred disorders often met with.* The excess of adrenoxidase is likewise shown by the tendency to thrombosis observed in these cases, adrenoxidase being, as we have seen, the blood's fibrin-ferment.*

The prolonged strain imposed upon the adrenal system finally causes it to become functionally weakened.* This condition is aggravated when the tumor is the seat of ulceration, by auto-intoxication, owing to the accumulation in the blood of detritus and bacteria from the putrifying mass. Death occurs, unless a fatal intercurrent disease appear, from asthenia, the typical mode of death when the adrenal center becomes paralyzed.*

The cancerous cachexia is now attributed to the direct action of poisons derived from the cancer upon the tissues, causing their degenera-

* *Author's conclusion.*
[93] Hemmeter: Amer. Jour. Med. Sci., Apr., 1903.
[94] Mayet: C. r. de l'Acad. d. sci., May 29, 1905.