The nature of the cancerous processes and the cancerous cachexia, and the relation of local irritation to each / by Roswell Park.

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THE NATURE OF THE CANCEROUS PROCESS AND THE CANCEROUS CACHEXIA, AND THE RELATION OF LOCAL IRRITATION TO EACH.[1]

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OVER one hundred years ago, a great, but in this country almost forgotten surgeon, Peyrilhe, voiced the following sentiment, which is just as true to-day as when he gave it expression: "*Ut cancrum curare, sic eum definire perarduum est*" (*Diss. de Cancro*, Toulouse, 1774). Every pathologist who studies the disease, and every surgeon who attacks it, will concede willingly that in order to cure cancer one ought to know the nature of the disease with which he has to deal; and every modern pathologist will also concede, I think, that oncology, with its kindred subject teratology, constitutes the most fascinating and important field for his labor.

Indeed so important, so difficult, so all-absorbing is the study, that some of us, who live in what I have nicknamed the actual tropic of cancer, succeeded in securing State aid in prosecuting it. Thus it came about that there was organized the State Pathological Laboratory of the University of Buffalo; and thus again, I take it, as one deeply interested in the movement, I have been invited to participate in this discussion this evening. That I may do justice, then, to the subject, as well as to myself, it seems wise to consider some of its clinical and border-line aspects, leaving a demonstration of methods and results to my colleague Dr. Gaylord, the head of the actual laboratory work.

When we deal with the matter and manner of growth of cancer we find that while in the minds of many karyokinesis undoubtedly plays a most important rôle, it is not the sole feature of interest in this connection. Even the abnormalities of mitosis, interesting as they may be, do not explain much of what we must appreciate in order to know in what the disease process consists. Arnold (*Virchow's Archiv.*, 1883–4) has called

1 Read before the New York Academy of Medicine, February 14, 1900.

attention to the frequency with which may be noted what he calls fragmentation of these tumors, which consists in a more or less regular division and segmentation into small masses or nodules, either with or without multiplication of tumor elements. Aoyama (*Virchow's Archiv.*, 1886) has maintained that these are post-mortem changes, since the figures and changes described by Arnold may be seen in various inflammatory conditions.

Another phenomenon observed by many, to which Klebs and others have attached considerable importance, is that of leucocytic inclusions, *i. e.* the penetration of leucocytes into the interior of the neoplastic cells. This, of course, is a common phenomenon in the infectious granulomata, and receives there a commonly accepted interpretation. No matter what importance there may be attached to it by others, it would seem to me that in a case of malignant tumor leucocytic invasion is equivalent to phagocytic, and can be viewed only in one light, *i. e.* as an effort at protection against invading organisms. The fact that the dead leucocytes are so often found in the tumor mass does not detract at all from the importance of such an explanation. Leucocytic aggregation and infiltration must here be regarded as a reaction from some form of irritation. Its recognition brings up again the constantly recurring question, Is cancer due to intrinsic or to extrinsic causes? Leucocytic invasion, *i. e.* phagocytosis, is practically always a reaction against extrinsic causes. As observed in carcinoma, and even more often in epithelioma, where leucocytes are seen in the interior of the pearly bodies, it is more than a mere reaction against the irritation of foreign bodies; it partakes of the significance of an active positive chemotaxis.

Surely surgeons generally have not attached sufficient importance to the facts so beautifully elaborated by Cornil and Ranvier, who have shown the wonderful freedom of communication between the minute terminal lymphatics and the alveoli of cancerous tumors. The possibility of lymphatic involvement is, of course, everywhere recognized, but the mechanism of it is not generally made clear enough, neither is the practical lesson to be derived from this anatomical fact.

Metastatic foci seem to evidence predilection for certain organs, depending upon the character of the growth. Certain cancers, for example, generalize themselves mainly through the osseous system, as, for example, in the cases studied by Leusinger (*Die Knochenmetastasen beim Krebs;* Inaug. Diss. Zurich, 1896), who found that in cancer of the thyroid 20 to 25% of metastases were found in the bones, in cancer of the breast about 14% and in cancer of the uterus only about 3%. Aside from the reports of individual cases by different observers, to which I could add several of my own, showing the tendency to osseous lesions in cancer of the breast, it is worth while to note Recklinghausen's statement, that secondary cancer of the bone is particularly common in primary disease of the prostate.

Secondary nodules in voluntary muscles at a distance are very rare, although Handford (*Trans. Path. Soc.*, London, 1888) and Menetrier) *Traite de path. gen. de Bouchard*, Tome III., 2, p. 748), have published cases of muscle involvement after primary cancer of the lung. In sarcoma, on the

other hand, pulmonary metastases are very frequent, as would be only expected on anatomical grounds. Mueller (*Beiträge zur Kenntniss der Metastasenbildung malignen Tumoren*, Inaug. Diss., Berne, 1892) has given us some very interesting statistics gathered from the records of the pathological institute in Berne for the thirty-five years previous to his publication. During these years 623 cases of malignant tumor came to autopsy, of which 521 were carcinoma and 102 sarcoma. Of the former metastases in the lymphatics occurred in about 50% of cases, liver 28%, peritoneum 24%, lung 12%, pleura 10%; while for the sarcomata the lungs were secondarily involved in 40%, the lymphatics in 30%, the liver in 12%.

It is worth while to emphasize that dissemination of malignant elements takes place not only with the ordinary blood current, but sometimes by means of retrograde venous embolism, (*Zahn, Virchow's Archiv.* 1889) for Zahn and Arnold (*Virch, Archiv.* 1891) have both reported instances of this kind, and the latter has provoked it experimentally by producing an excessive degree of pulmonary stasis.

Diffusion of cancer along nerve trunks is also extremely interesting and more common than is generally appreciated. Colomiatti (*Sur la diffusion du cancer le long des nerfs*, Turin, 1876), and Pelliet (*Cancer recidive du sein, propagations aux nerfs de l'aisselle, Bull. Soc. Anat.*, 1892) have shown how much of the pain in certain instances of cancer is due to invasion and involvement of nerve trunks by cancerous deposit.

Involvement of surfaces constantly in contact is known to afford frequent instances of transmission of cancer, particularly of epithelioma; as, for instance, about the mouth, the vulva, etc. Bergmann has emphasized the possibility of cancer from one lip to the other (*Deutsche Med. Woch.*, 1887). Simon and Shattock (*Brit. Med. Jour.*, 1888) and Newman (*Glasgow Med. Jour.*, 1888) have shown how the same thing occurs in the larynx.

Kauffman has seen cancer conveyed to the eyelid from the globe of the eye, and Fenwick has noted its transmission from one surface to another in the bladder. Constant and immediate contact is not always necessary for this purpose, as such lesions about the lip and tongue demonstrate. Further illustration of this kind of transmission are seen in cancer of the stomach, produced by swallowing cancerous vegetations from the esophagus, of which cases have been reported by Cornil, Klebs and Luecke, as well as by Menetrier. Cancer of the esophagus penetrating the trachea has also produced lesions in the lung by the same kind of mechanical transmission, while Schimmelbusch has reported cancerous infection of the lip through the finger-nails of the individual who was handling his cancerous ear. The very great importance to be attached to cancerous involvement of the track of an instrument cannot be overestimated. This has occurred numerous times after tapping the abdomen in cases of ascites due to cancer and in other parts of the body after various other kinds of instrumentation. Moreover, the cancerous elements when introduced into serous fluids seem to find there conditions favorable for their reduplication. Other instances, to which I have already called attention in previous papers, of unfortunate transmission of

cancer from one part to another of the human body, by the surgeon, might also be added, such as the case reported by Claude and Pilliet, where this result followed an autoplastic operation (*Bull. de la Soc. Anat.*, 1895).

As illustrating the defects of laboratory research in this direction, a very abbreviated list of those who have made various injection experiments and failed to secure positive results would begin at least with Peyrilhe, who, about 1772, injected cancerous juice into the veins of dogs, and thus instituted a series of experiments continued and modified by such eminent pathologists and surgeons as Dupuytren, Weber, Doutrelepont, Billroth, Lebert, Villemin, Tilanus, Klebs, Israel and many others. A list of failures by such eminent authorities proves not necessarily the impossibility of that which they were trying to accomplish, but rather the inutility of the methods adopted by them, as well as the extreme difficulty attending this line of investigation. Other observers, and for the most part much more recent, have obtained varying or questionable success, as for instance, Firket (*Semaine mèd.*, 1893), who thus produced sarcomata in a rat which killed the animal in five weeks, or Pfeiffer (*Die protozoen als Krankheitserreger*, 1891), who reproduced melanotic cancer from a primary cancer of the limb of a young girl, or Mayet (*Comptes rendus*, 1893), who used a glycerine extract of a mammary tumor and produced cancerous nodules in the kidneys of a rat, or Boinet (*Marseille mèd.*, 1894), who had about the same result. Much more successful, and only so as we appreciate conditions, are those experiments where malignant tumors have been transmitted from one animal to another of the same species. A number of observers have succeeded in efforts of this kind.

A growth of epithelioma upon lupus has been noted by numerous observers, and has been particularly studied in literature by Raymond (*Ann. de dermat. et syph.*, 1887), and Desbonnets (*Devel. de l'epithel. sur le lupus, Thèse de Paris*, 1894). This complication is never observed with lupus erythematosus but only after a true tubercular form, whether of the florid or the ulcerating type, or even after complete cicatrization. Of 90 cases collected by Desbonnets 21 concerned lupus scars, and in all the other cases the lesions were old before the epithelioma began to grow. It is difficult to fix the degree of frequency of this particular complication. Leloir (*Traité de la Scrofulo-tuberculose*) put it at 15 to the 1000, while Dubois-Havenith (*Thèse de Bruxelles*, 1890) oberved it five times in 118 cases of lupus.

In other cases also of tubercular primary lesions besides those of the skin which we call lupus, cancerous alterations may be met as later sequences or, as I would call them, secondary infections. Or they may more rarely appear almost coincidently.

Syphilitic lesions or their resulting scars may equally be points of departure for these cancers, either on mucous surfaces or in the viscera. They have been observed often in the mouth, upon the penis, the skin, the vulva and the testicle.

Fistulous tracts again, especially those leading inward from the skin, with a gradual downward extension

epithelium, have been the point of departure for numerous epitheliomata. Borchers (*Inaug. Diss.*, Göttingen, 1891) has reported five cases of cancerous fistula leading down to old bone disease, and Devais has collected 39 such observations, while Guiard (*Ann. des mal. des organes genito-urin.*, 1882) has published two cases of rapidly progressing epithelioma which had formed around old urethral fistulas.

Chronic suppurative otitis media has occasioned epithelioma of the ear in more than one known instance, like those reported by Kretschmann and Marchal (*Thèse de Paris*, 1895), while Mouchet has reported an epithelioma developing around the point of origin of a cutaneous horn (*Soc. Anat.*, 1894).

More common than any of these above mentioned forms are those connected with old scars, especially those so placed that their nutrition is always liable to disturbance. The most common are those produced by burns. I have, for instance, recently lost a patient who had an enormous epithelioma develop over the scapula in the cicatrix resulting from a burn, which necessitated the total removal of the upper extremity. He remained well for some years and then the trouble began recurring at different points in the old scar, and after repeated operations attained a degree of depth and extent which made it inexpedient to go further. He was under my observation altogether six or seven years. Volkmann found that among 164 cases of cancer of the extremity 126 of them were apparently due to previous irritation such as chronic ulceration, cicatrices, etc., all of which occurred where there had been papilomata or other congenital lesions, while only 27 had appeared without some previous explanation.

In this way I have laid stress upon the predominance of cancer in various parts of the body as a consequence of preceding irritation, such as may be caused by tobacco, disturbed salivation, burns, frostbites, constant slight traumatism, ulcerated epiblastic inflammatory lesions, syphilis, warts, ichthyosis, etc. The frequency of cancer of the tongue after psoriasis is universally acknowledged, occurring, according to Debove's observations (*Thèse de Paris*, 1873) 24 times out of 25 in men, a process quite similar to Paget's disease of the nipple. Moreover, isolated observations in this same general direction all have their own particular value; as, for instance, that of Helferich (*Deutsche med. Woch*, 1890), who saw cancer of the lip in a fisherman who constantly held some of his instruments in his mouth, and Hulke (*Med. Times and Gaz.*, 1873), who saw cancer in the palate following a local traumatism; or Kronacher, who observed the same thing after injury inflicted by a dentist; while all of us, dentists as well as surgeons, well know the frequency of cancer in the mouth as a result of an irritation produced by diseased and jagged teeth or by collections of tartar (*Deutsche Zeit. f. Chir.*, Vol. XXIX.).

About the vulva also, as about the tongue, trifling but chronic lesions may lead as well to epithelioma, of which many instances could be quoted. The so-called psoriasis uterina is an analogous condition of the uterine mucosa described by Zeller, which has given rise to cancer of the uterus in several reported instances, and it is almost

impossible to think of uterine cancer without thinking of some preceding and favoring lesion, like the use of a pessary, or many other things which will occur to all who reflect upon the subject. Bernard (*Thèse de Paris*, 1895) has reported in one thesis at least six cases apparently due to use of the pessary.

So, also, for the stomach. The relations which exist between round ulcer and subsequent cancer have been considered by many pathologists. In 1848 Dittrich collected 160 cases of gastric cancer, in eight of which he found old cicatrices of ulcers. Lebert (*Krankh. des Magens*) in 1878 reported a similar number of cases. The transformation of ulcer into cancer was particularly studied by Hauser, in 1883, who carefully described the changes in the gastric glands from normal to cancerous type. Heberlin estimates that 7% of gastric ulcers change later into cancer. Rosenheim puts this at 6%. Foreign bodies in the stomach producing traumatic ulcers have led also to the same result, as, for instance, in a case reported by Haslam (*Lancet*, 1889) where a piece of bone was arrested in the colon.

So, too, vesical calculi have produced sufficient irritation to lead to cancer, and there is strong reason to think that lithiasis, both renal and biliary, may produce malignant lesions. Of 48 cases of cancer of the gall-bladder collected by Zenker (*Deutsche Arch. f. Klin. Med.* 1889), in at least 41 of them previous gall-stone trouble could be positively made out.

Over a year ago I had occasion to remove a large cancerous gall-bladder with a considerable adjoining portion of the liver and found two large gall-stones, the larger of which was the size of a pullet's egg.

In other parts of the body, as well, this same sort of thing is noticed. Friedlander (*Fortschritte der Med.*, 1885), for instance, has seen epithelioma developed around the wall of a lung cavity, and Ohloff has described malignant alterations of the tracheal epithelium, from cylindrical to squamous, under the influence of irritation caused by the presence of the tracheotomy tube. He has, moreover, observed at least one case of epithelioma of the trachea subsequent to laryngeal lesion. Evidently, then, as determined by numerous observers, under the influence of constant irritation, cylindrical or round epithelial cells can assume the squamous type and give rise to squamous-celled cancer.

Moreover, in the respiratory organs we may see numerous examples of the effect of continuous irritation in the development of tumors. Thus Haerting and Hesse have described a form of tumor of the lungs almost peculiar to the miners of the Schneeberg, consisting of lymphosarcoma or endothelioma of the bronchial nodes and lungs, which seems to be due to the inhalation of the dust from the cobalt and arsenical ores which they are handling.

There are certain relations which exist also between interstitial nephritis and the formation of adenocarcinoma of the kidneys (Sabourin, Oettinger, Netter, *Rev. de Med.*, 1885), between renal lithiasis and cancer of the kidney (Shattock, Israel, Hartmann, *Progres med.*, 1886), between lithiasis also and cancer of the bladder (Roesen, *Münch. med. Woch.*, 1886), between chronic stricture of the urethra and cancer (Wasserman, *Thèse*

e Paris, 1895), and between lesions f the kidney, pelvis and ureters and he formation of cancer at these points, while Kundrat has described cancer f the renal pelvis following upon hronic pyelitis (*Semaine med.*, 891).

The liability, also, of benign tumors o undergo malignant transformation s of great importance in these con- iderations. This occurs more often pon epithelial surfaces, for example, kin, larynx, etc., and is perhaps seen nore frequently in tumors of the vas- ular type, such as naevi. They oc- ur sometimes spontaneously, *i. e.*, vithout known cause ; at other times s the result of irritation brief or pro- onged. Indeed, so frequent is this orm of degeneration that a few writers elieve that sarcoma has an essen- ially vascular origin. Occasionally he transformed tumor assumes the melanotic type, by which it acquires an added malignity. Naevi, however, are not the only tumors which under- go these changes. Fibroma mollus- cum, according to Chambard, gives rise to myxoma, while Rindfleisch, Mallassez, Pilliet and others have in- sisted upon the fact that it undergoes sarcomatous degeneration. Inasmuch as fibroma molluscum has a somewhat variable histological structure, it may present at some times myxoma- tous, cartilagenous or even bony char- acteristics, or at others evident malig- nant changes. The verrucose naevi are those which especially often un- dergo epitheliomatous changes. Thus, Renoul (*Thèse de Paris*, 1892) col- lected 121 cases of tumors of all kinds developed from naevi, 34 of which were epitheliomata. Melanotic can- cers may also spring from these naevi, but more often have their origin in those which were pigmented from the beginning. Xeroderma pigmentosa, according to Kaposi and Vidal, fre- quently changes into epithelioma. Sebaceous cysts and wens, even those of congenital origin, occasionally un- dergo these changes, Franke (*Archiv. f. klin. Chir.*, 1887) having collected 18 cases of this character.

In the mucous membrane of the ali- mentary canal similar changes are also observable, as, for instance, in the large intestine there has been observed hy- pertrophy of glandular structure amounting to polypoid outgrowth and then cancerous transformation of this hypertrophy (Bardenheuer, *Arch. f. klin. Chir.*, 1891). Hauser has de- scribed five cases of rectal cancer among 24 which he especially studied, which showed positively the co-exist- ence of cancer and rectal-polyps. The relations existing between cystadeno- ma of the ovaries or especially ovarian dermoids, and malignant degeneration are well known. These tumors are always of complex type, and seem to be peculiarly susceptible to the influ- ences which determine malignant changes. Orillard (*Soc. Anat.*, 1893) has described myxomatous metastases which accompany certain cases of this general character, while Fraenkel (*Wiener med. Woch.*, 1883) has especially noted the complex character of the secondary growths, which closely imitate the original structures. Uterine adenomata certainly predis- pose to cancer of the uterus, and co- existence of mucous polyps and of epithelioma is by no means common. Parallel with these epitheliomatous changes are also the sarcomatous de- generations which numerous observ- ers have noted in uterine myomata. Thus, Pilliet and Costes (*Soc. de biol.*,

1894 saw this occur 11 times in 21 cases.

And so one could spend much time and go over the various parts of the body, tracing how in every structure almost similar changes might be observed; as, for instance, in the thyroid, the salivary glands, the prostate, the adrenals, etc., ever coming back, however, to the essential facts above illustrated.

So far as transmission and inoculation from one to another animal of the same species are concerned, successful experiments have been relatively few in number, and yet they have been made abroad by Jeannel, Doutrelepont, Leblanc, Paul Bert, Rinne, Fischl and others. These also are in addition to those that I have alluded to in previous papers. Klencke has transmitted melanotic cancer from horse to horse, and Geissler has also succeeded with dogs in the same way.

Among all the consequences of various inoculation experiments, one should not forget certain phenomena well known to laboratory workers who employ the intravenous method of inoculation, which are seen more particularly among white rats than among other animals, in whom not infrequently, after intra-peritoneal inoculation, and sometimes later, usually two or three months, there occur relatively large nodes, usually softening at the center, accompanied by lymphatic involvement and enlargement both of the abdomen and thorax, and presenting every appearance of true tumor formation. A fragment of one of these masses inserted into the peritoneum of another will reproduce itself, and a series of animals may thus be infected one after the other. In reality these are granulomata of some kind, which show this tendency to softening in the interior, and which furnish from culture media abundant growth of microbes.

The cancerous dyscrasia so universally noted in cancer patients is quite analogous to the dyscrasias which predispose to other infections, and is a favoring cause rather than an unfortunate effect, since it precedes rather than follows many of these diseases. Even if one feels impelled to side with those pathologists who believe in the ineffectivity of epithelial cells, *per se*, we must still acknowledge a susceptibility of certain tissues to their invasion. This cancerous dyscrasia is without classic symptoms, and, in fact, cannot be as yet recognized, as one can recognize, for instance, the dyscrasia which predisposes to tubercle; and above all things it must not be confounded with the cancerous cachexia which, of course, is the result of the presence of the growth. The one is a forerunner; the other a consequence, and the two should never be confused.

In explanation of the latter, many views have been advanced. Some would explain it entirely on the hypothesis of disturbance of nutrition and perverted exchange, or exaggerated destruction of albuminoid materials. Others ascribe it to augmentation of reducing substances in the blood. Some find modifications of the urine upon which they would explain the alterations, as for instance, a diminution of urea, of phosphoric acid and of chlorides. The elimination of urea, however, is affected by too many other incidents to be positively influenced by the presence of cancer. At all events, it is not yet a safe guide to

gnosis, although, for my own part, d from a series of observations con- cted in my own clinic by some of my mer assistants, I have rather leaned the opinion that there is a diminu- n of urea in cases of cancer which not to be accounted for by dietetic riations. For most of us, however, e particular cachexia of cancer is be ascribed to a toxic agent directly nnected with the presence of the nor, whose absorption into the ganism produces the evident results. One must remember that injec- n of cancer juices into animals s produced most serious disturb- ce, and is sometimes rapidly fatal; pecially so in animals already af- cted with the disease. The exper- ients of Boinet and Pfeiffer have own that infusions of cancer tissue salt solution produce fever, sali- tion and even collapse. Freiere has lled birds by injection of cancer juice d F. Mueller has observed that the ood serum of cancer patients more uickly destroys albuminoid material an an equal injection of normal rum. Feltz has found the urine of ncer patients more toxic than normal rine, and numerous other observers ave proven the extra toxicity of such rine. Clinically, Gross has observed xceedingly rapid septic consequences, nd even that which he calls carcinom- tous coma, in consequence of rapid oftening of a malignant tumor, and Klemperer has reported two cases of oma in cancer patients strongly re- embling diabetic coma. He found a arked diminution of alkalinity of he blood, and discovered the presence f oxybutyric acid in the urine. Adamkiewicz has particularly insisted n the toxicity of cancerous products, maintaining that with these tumors there is produced a poison analogous to cadaveric poison, which kills animals in a few hours by causing paralysis of cerebral origin, which latter he could even produce by applying to the surface of the brain a portion of cancerous tumor. However, his experiments have been criticised by Hansemann and Geissler, in that he did not exclude in his experiments the ordinary septic accidents.

Enough has been said, however, to show that by numerous competent observers certain toxic phenomena are inseparably connected with the cancerous cachexia.

Bard attributes the cancerous cachexia to the absorption of the products elaborated by the cells of the tumors, which, according to him, amount practically to excess of only glandular secretion. Thus, he would describe the gastric cachexia, the pancreatic, etc. This theory is attractive in certain aspects, and yet probably has but little to sustain it.

"This condition, which is the ordinary cause of death in cancer, unless one of the great vital organs be seriously involved, or an artery eaten across, was for long a great puzzle, until it dawned upon us that the cancer-cell masses, having no ducts or proper excretory channels, were pouring their abundant waste products into the blood and lymph, thus poisoning the entire body, precisely as those vegetable parasites the bacteria do with their secretions or toxins."—Hutchinson.

Truth is, in all probability, that the cancerous cachexia is a complex product of numerous factors, including degenerative products both of the neoplastic cells and of perturbed action of normal cells, and of those accidental

disturbances of important organs which may be the result of mechanical obstruction; as, for instance, pressure upon the biliary passages in cancer of the pancreas, pressure upon the ureters in cancer of the uterus, etc. Moreover, we must not lose sight of the anemia consequent upon hemorrhages or disturbed nutrition, and of the secondary infections, mostly septic, which are likely when the growths are near or upon the surface, including the absorption of ptomaines, etc., under whose constant influence visceral degenerations may easily occur. Furthermore, frequency of renal lesions must not be forgotten, as, for instance, according to Schrader, parenchymatous nephritis occurred ten times in fifty cases of cancer of the stomach. Even this list is necessarily incomplete; nevertheless, it will show how many factors are to be taken into consideration in accounting for the reduced condition of the cancer patient, which will vary more or less according to the character and location of the tumor, visceral lesions producing them more rapidly than those of the connective tissue, and glandular cancers being probably the most fatal of all.

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[Those interested in this subject are invited to read also a paper by the writer entitled "Again the Question of Cancer," read before the Medical Society of the State of New York, January 31, 1900, and published in the *Medical News* for March 3, 1900. It is, in fact, the complement of the above paper which was read before the New York Academy of Medicine February 15, 1900, and the two should be regarded as constituting a single contribution to the subject of cancer.]