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CHEMOTHERAPY AND TUMORS *

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Within the last three years a number of reports have appeared in the medical press which bear on the treatment of malignant growths in human beings by chemical preparations. The most persuasive and the most insistent claims have been made in connection with the colloidal solutions of certain metalloids and metals, notably selenium, vanadium and copper. At the same time a number of drug houses both in this country and abroad have placed on the market proprietary preparations of these substances in various forms, for which the claim is made that they produce striking therapeutic effects and sometimes even cures in malignant neoplasms.

The impulse toward the use and production of this type of preparation is directly traceable to a series of scientific experiments on the tumors of animals, which date back no farther than the year 1911. In that year Wassermann and his co-workers[1] published a report on the treatment of rat tumors by means of the intravenous injection of selenium compounds. This paper received wide notoriety through its enthusiastic diffusion by the lay press. Shortly afterward Neuberg and his co-workers[2] published their observations upon the therapeutic effects of certain metallic compounds. The clinical application of the encouraging results obtained by these authors in animal tumors followed rapidly, and up to the present time a number of papers have appeared in which the claim is made that human tumors also may be favorably influenced through the constitutional use of substances similar to those used by Wassermann or Neuberg. In some cases, use has been made of colloidal solutions of the heavy metals such as copper; in others, selenium compounds have been used, while in a third set of observations the therapeutic agent represents an attempt to combine the virtues of these two types of therapy by employing selenium in colloidal form. As an example of the first class, may be cited the cuprase of Gaube du Gers;[3] of the second, the seleniovanadic ointment of Roemer and the sulpho-selene of Walker; of the third, seleniol and electro-selenium.

Inasmuch as this new type of cancer therapy derives its origin, its justification and its support, in very large measure, from the laboratory results obtained in animals, it is a matter of considerable importance to examine those results with care, in order to determine whether they furnish a satisfactory basis for human therapy, and whether they justify the hopes to which they have given rise.

It is safe to assert that the application of chemotherapy to the treatment of tumors practically dates from the publications of Wassermann. He stated the principle that a rational therapy of tumors must be based on constitutional treatment. It appears evident that local treatment can have only local effects. The lymphatic extensions of tumorous growths, and the often unsuspected metastases in distant organs must of necessity escape the effects of purely local treatment. Hence, Wassermann reached the conclusion that all treatment of cancer which was to be effective, and not merely palliative, must be carried to all parts of the body by means of the blood stream. He therefore introduced the use of intravenous injections in the experimental therapy of rat and mouse tumors. An accidental observation led him to believe that selenium was a substance possessing a high degree of affinity for tumor cells.

In order to insure the penetration of the tumor in the live animal by this substance, however, he considered it essential to combine it with some other highly diffusible substance. This type of substance, which was to act as a carrier of the selenium, he described under the name "cytotrochin," from the Greek word τροχιά, meaning road. For this purpose he selected eosin. The eosin and the selenium were then combined by a method and in a form the details of which have never been published. All that we know of this preparation is contained in the statement that it is very difficult to produce, and that it is extremely unstable and difficult to keep. Mice can be given amounts of from 2 to 3 mg. of this substance in solution. Wassermann experimented with mice inoculated with transplanted tumors of the types of carcinoma and sarcoma. After from three to five intravenous injections of the drug, he notes that the tumors become softer and fluctuate. After still further injections the fluid mass undergoes absorption, and the tumor gives the impression of an empty sac. If it is possible to carry the injections up to the number of ten or twelve, recovery ensues. In such cured animals there remain only the unabsorbed portions of the fibrous capsule. Recurrences were not observed in the cured animals. Wassermann further stated that two spontaneous tumors in mice which had been treated by this method presented favorable results.

Wassermann's original presentation gave few experimental details, and has not been followed by the promised scientific report. From his article it is impos-

* From the Cancer Research Service of the General Memorial Hospital, New York.

* This critical discussion of the status of chemotherapy in tumors was prepared at the request of the Council on Pharmacy and Chemistry of the American Medical Association.

1. Wassermann, Keysser and Wassermann: Deutsch. med. Wchnschr., 1911, p. 2389; Berl. klin. Wchnschr., 1912, p. 4.
2. Neuberg and Caspari: Deutsch. med. Wchnschr., 1912, p. 375. Neuberg, Caspari and Löhe: Berl. klin. Wchnschr., 1912, p. 1405.
3. Gers, Gaube du: La cuprase et le cancer, Paris, 1913.

sible to determine what proportion of his animals were cured and what proportion failed to survive the treatment. From a later paper by Keysser[4] we learn that by far the larger proportion of the animals perished during the treatment in the stage of softening, so that a cure was accomplished in from only 3 to 5 per cent. of the animals. This is a point of great importance, inasmuch as it furnishes an indication of the highly dangerous character of this mode of treatment. Fatal results are attributed by Keysser to the absorption of toxic products from the tumor. This contention, however, is supported by no observations, and it is certainly equally fair to assume that death results from the toxic effects of the compound. A microscopic study of tumors taken from animals undergoing treatment was made by Hansemann. He found that the death of the cells was the result of nuclear destruction.

Within a very few months of Wassermann's publication, Neuberg and Caspari[2] published a paper which was the first of a series of studies on the therapeutic effects of the heavy metals on the animal tumors. They used zinc, platinum, tin, selenium, copper, silver and cobait in the form of certain complex organic compounds, the composition of which is not revealed. Owing to the fact that intravenous injections of these compounds produced a specific effect on the tumors, they are described as "tumoraffin" substances. Immediately after the intravenous injection of these preparations, there followed a marked hyperemia of the tumor, whereas the remainder of the mouse's body appeared markedly anemic. The hyperemia was often attended by hemorrhage into the tumor. This first stage was succeeded by liquefaction and absorption followed by recovery in favorable cases. The authors failed to state in what proportion of their experiments the animals died, and in what proportion recovery ensued.

The second paper on this subject is by Neuberg, Caspari and Löhe,[2] in which further details are vouchsafed. They state that with the compounds used by them the toxic and the therapeutic doses approximate very closely, from which it follows that the treatment, as with the Wassermann method, results in a very high mortality. Smaller doses produce no therapeutic effect; on the contrary, they seem to act as a stimulus to the tumor, accelerating the normal rate of growth. Spontaneous tumors show similar effects, but no cures are recorded. Only in tumors in which autolysis is active *intra vitam* does the method exert any effect. Consequently the benign primary tumors of animals, such as fibromas, are not influenced by it.

Neuberg and Caspari are to a great extent responsible for the colloidal theory of treatment in tumors. Accepting the observations of Petri and others that the autolytic ferments in tumors are quantitatively greater and qualitatively different from those present in the normal tissues of the body, they venture the assumption that the process of recovery in the experimental tumors of animals is due to the self-digestion of the tumor by these ferments. Ascoli and Izar[5] had shown that such ferments are materially stimulated by the presence of metals, and more especially of metals in colloidal form. This contention is apparently in harmony with the well-established fact that certain colloidal metals of themselves are capable of acting under certain circumstances as ferments. Neuberg and Caspari were at first of the belief that the compounds produced by them circulate in colloidal form. Subsequently they stated that these compounds were crystalline substances, but they assumed, under the influence of the theoretical consideration mentioned above, that these substances are broken up in the tumor and there undergo transformation into the colloid state.

In connection with the preceding observations there are certain other experimental results which require mention. Izar[5] succeeded in curing rat tumors by means of injection of colloidal sulphur. C. Lewin[6] cured subcutaneous mouse tumors with various preparations of gold. Werner and Szécsi[7] produced similar results through a combination of selenium-vanadium with cholin-borate; in these experiments the selenium-vanadium was supposed to be present in colloidal form.

Within a comparatively brief period of time, therefore, it fell to the lot of a number of observers, using strikingly different substances, to produce therapeutic effects amounting in a certain percentage of cases even to cure in the experimental tumors of the lower animals. The various procedures have little in common. Both metals and nonmetallic substances have been employed either in colloidal form or in combination with organic radicals. In some instances a diffusible carrier is combined with the basic substances; in others not. All of the preparations appear to possess a high degree of toxicity, although adequate data on this very essential feature are almost invariably withheld.

Wassermann's results with eosin-selenium were soon critically examined by other observers. Uhlenhuth[8] and Contamin[9] were unable to confirm his observations, but their negative results are attributed by Keysser to the fact that they were not in possession of the proper formula for the preparation of the eosin-selenium compounds as used by Wassermann. Apolant,[10] however, in Ehrlich's name confirmed Wassermann's findings.

The most important critique of eosin-selenium has been contributed by the subsequent investigations of one of Wassermann's original collaborators, F. Keysser.[11] Keysser's publication contains a large number of very careful observations on the various forms of eosin supplied by the German manufacturers, as well as on other matters which cannot here be considered in detail. He finally reached the conclusion that the eosin furnished by the manufacturing house of Sandoz was the most effective for his purposes, inasmuch as it combined the lowest grade of toxicity with the highest capacity for discoloring the tissues. The selenium, he used in the form of seleno-vanadium furnished by Clin of Paris, which was the identical preparation used by Werner and Szécsi in combination with borcholin. The maximum dose of this selenio-vanadium is 0.06 c.c. for each gram of mouse. Eosin, 0.01 gm., dissolved in 0.5 c.c. of physiologic salt solution, is mixed with 0.5 c.c. of the selenio-vanadium. This

4. Keysser: Wien. klin. Wchnschr., 1913, p. 1664.
5. Izar: Ztschr. f. Immunitätsforsch., 1913. Izar and Basile: Berl. klin. Wchnschr., 1913, p. 1312.
6. Lewin, Carl: Berl. klin. Wchnschr., 1913, p. 147; Berl. klin. Wchnschr., 1913, p. 541.
7. Werner and Szécsi: Ztschr. f. Chemotherap., 1913, Orig., i, 358. Szécsi: Ibid., ref., 1913, ii, 1060.
8. Uhlenhuth, Dold and Bindseil: Ref., München. med. Wchnschr., 1912, p. 1782.
9. Contamin, Detoeuf and Thomos: Bull. de l'assn. franç. pour l'étude du cancer, vi, 62.
10. Apolant, H.: VI Tag. der freien Vereinigung für Mikrobiologie., Berlin, 1912. Ref. München. med. Wchnschr., 1912, p. 659.
11. Keysser, F.: Ztschr. f. Chemotherap., 1914, Orig., ii, 188.

mixture is then used for intravenous injections. The results produced by the injection of this mixture are to all intents and purposes similar to those obtained by Wassermann, except that Keysser induced cure in a larger proportion of animals, namely, from 6 to 8 per cent. It is evident from his careful description of his experiments that the treatment is extremely toxic to the animals. The therapeutic dose is considerably greater than one-half the toxic dose. This accounts for the fact that an extremely large proportion of the animals perish during the course of the treatment. The tumors failed to be influenced unless the dose given fell very little short of the fatal amount. Moreover, in order to accomplish a complete cure, at least eight to ten injections must be given, and in some instances not less than fourteen.

Keysser's most important conclusions, however, were obtained by following an altogether different line of procedure. It had been pointed out by Carl Lewin[6] that the therapeutic results obtained from subcutaneous mouse tumors, however encouraging, could not be logically applied to the treatment of human cancers. The subcutaneous transplanted tumors, as is well known, are as a rule limited by a distinct capsule and show no tendency to infiltrative growth. In this particular they present a most striking difference when compared with human tumors. On the other hand, the metastases of mouse tumors in the internal organs present an infiltrative mode of growth and thus approximate very much more closely to the human type of tumors. Keysser therefore determined to test the therapeutic effectiveness of his compounds on tumors implanted in various organs. He developed a technic which enabled him to implant tumors in the liver, the spleen, the kidneys and other parts of the mouse by means of injection through special needles, often without the assistance of a cutting operation.

The tumors so implanted grew rapidly, and within from two to three weeks reached the size of cherry pits. The growth was characteristically infiltrative. Animals with these tumors were then submitted to intravenous injection of the therapeutic agents in exactly the same fashion as the animals carrying subcutaneous tumors. The results, however, were absolutely different. Whereas the subcutaneous tumors invariably showed a much more intense discoloration than the other tissues of the mouse, this feature was entirely lacking in the case of the internal tumors. Softening and liquefaction, which almost invariably follows on the third or fourth injection in the case of subcutaneous tumors, and which is the first symptom of cure, never presented itself in the case of the internal tumors. Their consistency throughout the treatment was indistinguishable from that of the tumors of control animals. The treatment, in fact, appeared to exercise not the slightest influence on internal tumors. There was neither cessation nor retardation in growth, but the tumors continued their normal rate of destructive increase with the production of metastases, leading eventually to the death of the animal either during the course of the treatment or shortly thereafter. Microscopic changes, such as had been observed by Hansemann in the case of subcutaneous tumors, were entirely lacking. No matter in what organ the tumors were implanted, these results remained the same. No matter what type of tumor was employed, whether carcinoma, adeno-carcinoma or sarcoma, the therapeutic outcome was regularly and consistently nil.

These results induced Keysser to determine whether or not eosin-selenium could actually be shown to exercise a deleterious effect on cancer cells outside the body. In order to do this he made a suspension of mouse tumor cells in salt solution and mixed this with the eosin-selenium-vanadium, using the latter in amounts equivalent to three times the fatal dose for a mouse. After the mixture had stood from one to three hours, it was injected either subcutaneously or intravenously into mice in order to test the vitality of the cells. In every instance the injections resulted in the production of tumors which could be in no way distinguished from the tumors produced by untreated cancer cells. In other words, the therapeutic preparation had absolutely no effect on the tumor cells.

In the same way Keysser carried out experiments along the lines inaugurated by Neuberg, using a combination of glycocoll and copper. He also tested the combination of borcholin with selenium-vanadium used by Werner and Szécsi. He was able to confirm the fact that both of these substances produced an unmistakable therapeutic effect on subcutaneous tumors. On the other hand, they were absolutely without influence on the internal tumors. In this respect, therefore, they were entirely comparable with the eosin-selenium compound. The theoretical basis constructed by Neuberg, which rests on the assumption that the metallic compounds stimulate autolytic processes in the tumors, was also subjected by Keysser to destructive criticism.

Finally, Keysser showed that none of these therapeutic agents were effective even in the case of subcutaneous tumors, unless the latter had reached at least the size of cherry pits. If a therapeutic injection were made immediately after inoculation of the tumors, no effect was observed. The tumors grew exactly as in the controlled animals, and died in about the same period of time as they.

All of these facts, which taken together constitute a very remarkable and convincing piece of scientific investigation, permit of but one conclusion. It is quite clearly established that none of the preparations of which the therapeutic effectiveness has hitherto been proclaimed exercise any direct influence on the life or development of the tumor. Under certain very definite and restricted conditions, however, they do appear to produce certain changes in the tumors, and in a small proportion even cures. These results, however, are obtained only in the case of tumors which are subcutaneous in location and not smaller than a cherry pit in size. Keysser's interpretation of the striking differences between the effects observed in the subcutaneous and in the internal tumors is of interest in this connection. He believes that the constant palpation and examination of the subcutaneous tumors, which is prompted by interest in the experiment, produces circulatory changes with hyperemia and hemorrhage. These circulatory changes are responsible for the increased tendency of the injected substances to lodge in the tumors, thereby possibly increasing the tendency to autolysis which the circulatory changes have inaugurated. It is, of course, questionable whether this explanation can be regarded as final. In a series of experiments which I performed many years ago, I was able to show that sodium iodid when injected intravenously accumulates in tumors in larger amounts than in any other tissue of the body in rats. A similar observation has been recorded by Wells, de Witt and

Corper.[12] In the same way I found that various dyes, such as Congo red, when injected intravenously, could be demonstrated in tumors long after the rest of the body had recovered its normal color; the liver alone vied with the tumors in this respect. The dyestuff was invariably sharply localized in the necrotic portions of the tumor. The conclusion seemed obvious that, owing to circulatory conditions or possibly even to chemical conditions, the dye was retained longest in the necrotic parts of the tumor. This effect was unquestionably not due to handling, inasmuch as the animals in my experiments were not palpated from the time of injection until death.

I have, however, had an even more striking demonstration of the same fact. I have given intravenous injections of dyes to patients suffering with various forms of internal tumors, as, for example, cancer of the breast, in the hope of favorably influencing the growths. At operation, the picture presented by the tumor is striking in the extreme. It presents areas of various size which are intensely discolored by the dye. These areas, both to the naked eye and under the microscope, are the necrotic parts of the tumor. The actively growing areas of tumor tissue and all the normal tissues of the organ present their normal color. All of these observations lead to the conclusion that the necrotic areas in tumors either possess a higher affinity for sodium iodid and for the dyes than do the normal tissues, or that these substances are more slowly absorbed from the necrotic areas owing to the circulatory deficiency. Whichever of these explanations be accepted, it is quite reasonable to believe that necrotic areas might well undergo liquefaction under the influence of the various substances which have been used for therapeutic injection. Such a result is, of course, without direct effect on the growth or vitality of the living part of the tumor. This fact is quite clearly evidenced by the experimental data, which show that the internal portions of the tumor might undergo liquefaction and yet the tumors were not cured. Indeed, Löhe, who made microscopic examinations of the tumors treated by Caspari and Neuberg, states particularly, with reference to a tumor which had been subjected to treatment, that "the central portion of the tumor showed softening, while the external margin was composed of actively growing cells." The central portions of implanted tumors are, of course, those which first undergo spontaneous necrosis.

It still remains to explain the small percentage of cures achieved by Wassermann and by Keysser. It does not appear to me that this problem presents any insuperable difficulties. The fact must be emphasized that practically 95 per cent. of the animals die under the treatment, which sufficiently indicates the toxic effects of the agent used. We must remember that transplanted tumors are under all circumstances at a certain disadvantage as compared with the normal tissues of the body. After all, they are implanted on a foreign soil. Their blood supply is impoverished and imperfect. They have a natural tendency to undergo necrosis, and in many cases spontaneous retrogression. It is not strange, therefore, that they should prove in slight degree more susceptible to toxic effects than are the normal tissues of the body.

If we remember that the various therapeutic agents introduced in all probability reach a somewhat higher degree of concentration in the necrotic areas of the tumor than in the normal tissues of the body, an assumption which is entirely in accord with the facts as observed in the case of sodium iodid and of various dyes, we may be quite prepared to believe that this factor is sufficient to induce the destruction of the marginal healthy and living cells of the tumor. The fact that small subcutaneous tumors were found by Keysser to be entirely refractory to the treatment is entirely in accord with this assumption, in view of the fact that tumors of this size present practically no central necrosis. The same explanation holds of the observation previously cited from Caspari that the primary spontaneous tumors of animals do not yield to the treatment. Indeed, he himself states that the treatment is effective only in tumors in which autolysis takes place during life. The word autolysis, however, in this connection is a misnomer and represents a gratuitous assumption; as an actual fact, one is entitled to say only that such tumors undergo central necrosis, in all probability owing to defective circulatory supply. The process is exactly similar to the coagulation necrosis described in the case of tubercles by Weigert. If autolysis occurs it is only secondary to the preceding necrosis.

This explanation, however, is confronted by the fact that the internal tumors produced by Keysser showed no tendency to effect a localization of the dyes, and correspondingly no tendency to be affected by the therapeutic agents. One might be permitted to inquire whether these internal tumors had undergone any necrosis. Keysser unfortunately makes no mention of this matter. It is certainly true that the infiltrative mode of growth of the internal tumors, which is entirely different from that of the subcutaneous implantations, is associated with a much better blood supply and a lessened tendency to undergo necrosis. That such tumors can undergo necrosis, however, is evidenced by certain illustrations given by Carl Lewin in his paper on internal tumors. But such changes usually occur only in advanced stages. To judge from his plates, Keysser worked with relatively small tumors, an assumption which is rendered even more likely by the fact that his injections were undertaken in a fairly early stage of their growth. In this connection I may quote certain experiments of my own on internal tumors.* The implantations made in my experiments were produced by intravenous injections of a tumor suspension into the jugular vein of rats. Such injections resulted almost invariably in the production of a large number of tumors in the lungs, which, as is well shown in the figures accompanying the original article, differed very markedly in size. The smaller of these tumors are composed throughout of actively growing cells, while the large tumors present an area of central necrosis exactly as do the subcutaneous tumors. If such an animal be given an intravenous injection of a dye such as Congo red, it will be found that the larger tumors present an area of central discoloration corresponding to the area of previous necrosis, while the smaller tumors, like the normal tissues, are not colored. Thus, it is clear that the internal tumors implanted in animals are subject to the same laws concerning the distribution of dyes and, of course, other substances as are the subcutaneous tumors. As I have stated previously, an exactly analogous observation has been made in a human breast tumor. In the absence of any contradictory evidence, therefore, I think that it is perfectly justifiable to

12. Wells, H. G., De Witt, and Corper: Ztschr. f. Chemotherap., 1914, Orig., ii, 110.

* Jour. Med. Research, 1913, p. 497.

assume that Keysser failed to achieve a result in the internal growths simply owing to the fact that those growths presented practically no areas of necrosis at the time of his injections.

Another theoretical question which bears closely on the recent therapeutic investigations in human beings concerns the rôle of colloids as such in the procedure. It is quite clear from what has already been said that all experiments with animal tumors have been largely influenced by the belief that metals in the colloidal form exercise a peculiar and characteristic influence on the destruction of tumors. Even where the therapeutic agents have been introduced in crystalline form, as by Neuberg and Caspari, the authors find themselves compelled to assume that the metals are reduced to colloidal form within the tumors. For the latter assumption there is absolutely no evidence; it is due simply to the influence of the colloidal theory. If one critically examines the data on which this theory is based, one is forced to the conclusion that it has practically no established claim to validity. If we grant that colloidal metals have been shown to stimulate autolysis in the test tube, the same fact must be admitted of metals in noncolloidal solution. The experiments, however, are very far from establishing either of these facts satisfactorily. But even were this the case, it is an unjustifiable inference that living tumor cells would be influenced in anything like the same manner as are the dead cells observed in test-tube experiments. As an actual fact, we know from the work of Evans and Schulemann that only the "scavenger cells" of the body take up foreign colloids, and to this class the tumor cells do not belong. Moreover, the form in which metals are introduced into the circulation is not necessarily or even probably the form in which they act on the tissues. Colloidal solutions of the metals are certainly subject to precipitation and other changes on entering the blood. This fact I have shown experimentally in a previous study on colloidal copper.[13] In the same way it is probable, as has been pointed out by Wells, that metals when introduced in crystalloid form may rapidly be altered so that they are carried throughout the body in colloidal form. All of these considerations indicate how unjustifiable is the assumption that colloidal metals exercise a peculiar action on growing tumors. It is hardly surprising that their empiric use has failed to measure up to expectations based on so slim a foundation of fact.

CLINICAL OBSERVATION

Clinicians have not been slow in following the lead suggested by the therapeutic experiments in animals. It is perfectly proper that this should be the case. In dealing with a disease of the character of cancer, in many instances entirely beyond our power to influence, no one can question the advisability of trying any and every agent which holds out the slightest promise. Unfortunately a closer analysis of the animal experiments fails to vindicate even that degree of faith. When one considers the facts which have been analyzed in the preceding discussion, it would appear not only futile but actually dangerous to attempt to benefit cancer sufferers by means of any of the agencies which have been employed in animal experimentation. Nevertheless, the fact remains that a variety of preparations have been used in the human clinic. The various types of preparations may be satisfactorily grouped under four classes, namely:

1. The crystalline salts of selenium.
2. Selenium in colloidal solution.
3. Other metals in colloidal solution.
4. Compounds of metals with organic radicals.

These substances have been administered by injection or by the mouth. In the case of injection, the injections have been made either into the subcutaneous tissues, intramuscularly, or intravenously, or finally, directly into the tumors. Before passing to a further consideration of this subject in detail, it may be well to recall the fact that in the experimental tumors of animals, no matter what preparation has been used, it has been possible to accomplish therapeutic effects only by the use of relatively enormous doses of the medicament, of doses, in fact, which were scarcely lower than the lethal dose. Certain experimenters have noted that smaller doses actually stimulated the growth of the tumors. In the second place, it has almost invariably been found necessary to administer the treatment intravenously, inasmuch as the other modes of administration failed of therapeutic effect. It is quite apparent that a procedure in human beings in any degree analogous to that pursued in animals is entirely impossible. The doses used, with one notable exception to be subsequently mentioned, have invariably been relatively small. Hence it is apparent at the outset that at least one fundamental condition of success in the treatment of animal tumors has been necessarily excluded in the clinical applications.

The salt used by Wassermann is not stated in his original publication. Wolff[14] speaks of it as a sodium salt, whereas Keysser says that it was a combination with potassium cyanid. In only one instance, as far as I am aware, has the sodium salt been used therapeutically in human beings. Delbet[15] states that he employed this salt intravenously in one case, and that its use was shortly followed by death. Unquestionably the salts of selenium are very much too toxic to be used in this way.

The majority of those who have worked with selenium have used it in colloidal form, either preparing it themselves or employing one of the preparations put on the market by the pharmaceutic firms. Of the latter the best known are the electro-selenium of Clin, and the Seleniol of Couturieux. Of those who have made use of selenium in these forms may be mentioned Cade and Girard,[16] Bougeaut and Galliot,[17] Blumenthal,[18] Thiroloix and Lancien,[19] Delbet, Laurent and Bohec,[20] and most extensively of all, M. Touche.[21] All of these authors have described cases of malignant new growths of the most varied character which were treated by these preparations.

The results obtained are fairly concordant. The intravenous injection of the preparation produces but slight disturbance. There is leukocytosis, a moderate rise of temperature, and not infrequently a chill. Otherwise the substance seems to possess no toxicity.

13. Weil, Richard: The Effects of Colloidal Copper with an Analysis of the Therapeutic Criteria in Human Cancer, THE JOURNAL A. M. A., Sept. 27, 1913, p. 1034.

14. Wolff: Die Lehre von der Krebs Krankheit, iii, b, 1913.
15. Delbet, P.: Bull. de l'Assn. franç. pour l'étude du cancer, 1912, v, 121; ibid., 1913, vi, 85.
16. Cade and Girard: Bull. Soc. méd. d. hôp. de Lyon, 1912, xi, 397.
17. Bougeaut and Galliot: Clinique, Paris, 1912, vii, 501.
18. Blumenthal, A.: Jour. méd. de Bruxelles, 1912, xvii, 325; Presse méd. belge, 1913, lxv, 919.
19. Thiroloix and Lancien, A.: Bull. et mém. Soc. méd. d. hôp. de Paris, 1912, xxxiii, 197.
20. Laurent, M., and Bohec, J.: Med. Press and Circular, 1912, xciv, 461.
21. Touche, M.: Bull. et mém. Soc. méd. d. hôp. de Paris, 1913, xxxv, 451.

The effects produced on the tumors have almost invariably been described as encouraging. Touche, who treated twenty-seven cases in this way and has described each case in detail, states that under the treatment the surface of the tumors, if ulcerated, became cleaner and healthier; the tumors became softer; the rate of growth was arrested, and there was relief of pain and of the accompanying functional disturbances; often, too, there was a gain in weight and an improvement in general wellbeing.

Touche concludes his article with the statement that "it is certain that the effect is not curative, but it is actually palliative." Delbet, on the other hand, states that he has seen no beneficial effects from the use of colloidal selenium injected intravenously. In the discussion on Delbet's paper, Ledoux-Lebard states that he has observed nothing from selenium further than the temporary improvement which is shown by almost all cancer cases on the application of any new therapeutic measure. In one or two instances the claim is made in the literature of an actual cure of malignant growth through the use of selenium. Such for example is the case described by Blumenthal. From the clinical description this might have been a cancer of the tongue, and was judged to have been such in view of the negative Wassermann. No microscopic examination was made. Salvarsan was given. The patient recovered. It is clear that instances of this type cannot be accepted as beyond criticism, and it is safe to say that nothing more convincing in the way of actual cure is offered in the rather voluminous literature on the use of selenium.

Numerous compounds of selenium, some of them claiming to circulate in colloidal form, have been described, and have been put on the market for use in malignant disease. Such are Walker's sulpho-selene, and selenio-vanadium, which has been prepared in the form of an ointment by Schering and Glatz. These preparations lay claim to the same palliative effects which have been previously described for colloidal selenium.

Of the other metals in colloidal form, chiefly silver and copper have come into use. Colloidal silver was first recommended for malignant growths by Vogel. It is obtainable on the market in proprietary form under the name of fulmargin, and also as electrargol. Recently Rohdenburg[22] has made a careful study of the effects of colloidal silver in experimental and in human tumors, and finds that they have no value. Colloidal copper has been used in recent times for the same purpose by Gaube du Gers and by others. I have recently examined the effects of colloidal copper on malignant tumors in man, and have been unable to find that it has any therapeutic value. Furthermore, a study of the distribution of the copper in tumors obtained at operation or by necropsy from individuals so treated failed to show that the copper had been deposited therein.

Finally, preparations similar to those used by Werner and by Caspari in animals have also been used in human beings. In these cases also the authors have been able to record palliative effects on the tumor, but in no instance cures.

We have seen that it has been quite impossible to duplicate in human beings the therapeutic technic employed in animal experiments. We have seen further that the use of a modified technic in animal experimentation has never been productive of favorable results even at the hands of enthusiastic adherents. In striking contrast to these conclusions are the observations made in human therapeutics. For every type of preparation described in the preceding paragraphs, the claim has been made practically without exception that it exercises a markedly beneficial effect on malignant disease in the human being. Not only are the subjective symptoms alleviated, but also the tumors appear to become cleaner and softer; the rate of growth is retarded; necrosis and metastasis are prevented, and inoperable tumors become operable. How are we to interpret these observations? How are we to explain the fact that they are the almost invariable accompaniment of the most diverse methods of treatment? I have already quoted the statement of Ledoux-Lebard that every therapeutic novelty appears to exercise a favorable effect on cancer cases. The same fact has been observed in a variety of other diseases, such as locomotor ataxia.

In order to arrive at a safe and reliable estimate as to the value of any new or experimental procedure in cases of cancer, it seems advisable to accept certain definite therapeutic criteria by which the cases are to be judged. In the absence of such a method, alterations in symptoms which are actually of no real value or importance receive undue emphasis. The natural course of the disease is associated with such fluctuations that a sanguine therapeutist can gain some encouragement from even the most hopeless cases. Hence it follows that every mode of treatment has found adherents. The market is flooded with cancer drugs, and cancer charlatans flourish in the most highly educated communities. Unfortunately even well trained, honest and reputable physicians have fallen victims to this fallacy, and have lent their names to the support of modes of treatment which in reality produce no determinable effect on the natural evolution of the disease. It was the desire to combat this unfortunate tendency which led me some time ago to attempt to establish a reliable set of criteria of therapeutic effects in cancer. These were embodied in an article[13] which appeared two years ago, and I may be here permitted to quote them *in extenso:*

CRITERIA OF THERAPEUTIC EFFECTS

In determining the effects of any given mode of treatment on a tumor, a variety of criteria may be relied on. Circulatory changes in the tumor, the relief of pain and the restoration of a secondarily impaired function are certain of the criteria on which stress has been laid by the majority of observers in the past. Important as are these criteria in determining the progress of purely inflammatory processes, it is unquestionable that their value in judging of the effects of therapeutic methods when applied to malignant disease is open to criticism. It is a curious and interesting fact that almost every therapeutic claim made in recent years in connection with cancer has included among its virtues the relief of pain. This is true of vaccination with cancer tissue, of Hodenpyl's method and of many others. In view of this very general effect, not much stress can be laid on this symptom, and it is probably fair to assume that in the great majority of these cases the result is in no small measure psychic. The improvement of function is also largely a subjective phenomenon, and as such requires most careful criticism. Osler relates that he has known a patient with gastric cancer to be relieved of digestive disturbances and to gain 18 pounds in weight as the result simply of the visit of a sanguine consultant who denied the presence of a tumor. Improvement in the ability to chew food, to articulate words or to move a limb are phenomena familiar to those who attempt to treat cases of cancer. The victims of this disease

22. Rohdenburg, H.: Jour. Med. Research, 1915, xxvi, p. 331.

seem to be in a very high degree "suggestible" and impressionable and respond nobly to every therapeutic effort.

Circulatory changes in tumors offer an interesting group of clinical symptoms. The observation has often been made, especially in ulcerated new growths, that treatment is associated with swelling, peripheral hyperemia, and an altered character of the discharge. In spite of the fact that there is no reasonable relationship between this congeries of symptoms and the actual cure of the tumor, they generally receive considerable emphasis and are cited as an indication of the specific local action of the agent employed. It is also true, however, that the growth may continue to advance in spite of their presence. It is of some importance to inquire into the mechanism which produces these circulatory changes and into their clinical interpretation. It is a well-known fact that many drugs, when introduced into the body either by the mouth or through the skin, are excreted not only by the normal channels of elimination, such as the kidney or the intestine, but also from such ulcerated surfaces as may be present on the body. This is easily shown to be true, for example, of certain of the anilin dyes, which, when introduced by way of the veins, produce an intense discoloration of the dressings over ulcers. It is likewise true of certain of the metals, such as arsenic. In order to understand the series of events previously enumerated it is therefore only necessary to assume that the therapeutic agent is excreted from the ulcerated surface of tumors. If an irritant, it will tend to produce hyperemia of the margins of the ulcer, and an increase of the secretions. If an astringent, however, it may produce just the opposite of these effects. Such a result, however striking, is purely accidental, and has no necessary bearing on the growth or destruction of the tumor itself. It constitutes a symptom on which no reliance should be placed.

Excluding from consideration all of these secondary factors, we may conclude that the observation of the size of the tumor itself is the sole criterion on which we can place reliance in judging of the effect of therapeutic measures. This implies, in the first place, that a tumor must be accessible to fairly accurate measurement. Tumors of the uterus, for example, and intra-abdominal growths will only exceptionally fall into this class. In the second place, indirect evidence of a decrease in the size of tumors, such as is afforded by the increased permeability of obstructed passages, as in the case of tumors of the esophagus, pylorus or intestine, must be accepted only with great reserve. Remissions in the obstructive symptoms characteristic of such tumors are a frequent feature of the normal evolution of the clinical history of such growths. The relief of obstruction, however, may be due either to necrosis of the obstructing portions of the tumor, while the remainder continues to grow progressively, or to a relief of the accompanying muscular spasm. Finally, evidence of decrease afforded by the roentgenogram is not sufficiently exact in most cases to afford ground for so important a conclusion as that at present in question.

Not only must there be unquestionable evidence, however, of the diminution in size of the tumor, but this diminution must be of a kind not ordinarily attributable to the natural evolution of the tumor. . . . It is safe to say that multiple tumors offer enormous difficulties in the matter of interpreting therapeutic results. At present we have in the wards of the hospital a patient with multiple metastatic carcinomas of the skin. For several months we have at intervals made accurate measurements of certain of these tumors and have found that some have undergone retrogression, others have entirely disappeared, while still others have continued to grow steadily. In the case which afforded the ascitic fluid used in Hodenpyl's experiments, many of the lymphatic metastases underwent complete retrogression, while the metastatic process in the liver, as was demonstrated at necropsy, increased progressively, and ultimately almost destroyed that organ. Thus, in multiple carcinosis, the retrogression of individual nodules is no indication that therapeutic intervention has produced an improvement.

I shall not delay to emphasize those variations in the size of solid tumors which accompany hemorrhage and its absorption, edematous swelling, necrosis in the depths, and other familiar factors which clinically simulate, or induce, the softening and the reduction that are so often attributed to therapeutic interference. But it is important to draw attention to a similar feature in that type of superficial epithelioma known as rodent ulcer. These new growths not infrequently advance at one point of the periphery, while they recede at another, and thus cicatrization and contracture may simulate a partial recovery. This effect is due in part to alterations not in the growth itself, but in the accompanying ulcerative process. The secretions from the growths, especially if confined under dressings, may have eroded and destroyed the surrounding skin, and it is tempting to interpret a recession of the associated ulcerative disease as an indication of a favorable effect on the new growth. It is unquestionably this aspect of rodent ulcers which plays so generously into the hands of the numerous nostrum venders for this disease.

In brief, the demonstrable reduction in size of a tumor, of a kind not to be attributed to the natural processes of evolution of that tumor or of its associated lesions, is the one essential feature of effective therapeutic intervention.

When the various methods of treatment which have been discussed in this paper are judged by the standard advocated above, it is apparent that none of them can lay claim to therapeutic effectiveness. The modifications of the disease attributed to them are modifications which occur spontaneously in a very large proportion of cases as a result of the natural evolution of the disease process. This is a fact which cannot be too strongly emphasized. Owing unfortunately to the hopeless character of cancer, men are not prone to study with care all the lesser changes which the disease and the patient present under ordinary conditions; but when a "cure" is under investigation, the patient and his medical attendant note every apparent improvement with painstaking attention and enthusiasm. As a result, some evidence of improvement in treatment is entered on the books.

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THE SIGNIFICANCE OF BACILLUS COLI IN PASTEURIZED MILK*

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The presence of *Bacillus coli* or of any other nonsporulating gas producer in pasteurized milk is usually taken to indicate either improper pasteurization or subsequent contamination of the milk. For according to most authorities the thermal death points of *B. coli* and similar organisms are below the temperature of pasteurization. Thus Kolle and Wassermann[1] give the following summary of the various findings for *B. coli* up to the year 1903:

C	Minutes	
62-63	1	Von Geuns
59	5	Von Geuns
60	15	Kitasato
60	10	Weisser
60-61	5	Chantemesse and Widal
59	15	Chantemesse and Widal
55-60	120	Fränkel

However, more recently De Jong and De Graef[2] have described seven strains of *B. coli* which survive 65 to 67 C. (149 to 152.6 F.) for thirty minutes in milk or broth. These strains would not be killed by the degree of heat commonly used in pasteurization and

* From the Laboratory of Bacteriology and Hygiene, Johns Hopkins University.

1. Kolle and Wassermann: Handb. d. Path. Mikroorg., 1903, ii, 385.
2. De Jong and De Graef: Quoted by Rullmann, Centralbl. f. Bakteriol., Part 2, 1914, xli, 269.