A STUDY OF GENERAL AND LOCALIZED EFFECTS OF INTRAVENOUS INJECTIONS OF COLLOIDAL COPPER AND CASEIN IN CASES OF HUMAN CANCER *

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I. INTRODUCTION

In several brief communications¹ we published previously our observations on the effect of intravenous injection of colloidal copper in patients suffering from cancer. We also referred to experiments in which we used solutions of casein. We limited ourselves on those occasions to a brief report of some of our conclusions and referred to our future more detailed publication for a discussion of various results and problems of which we could not treat in our preliminary notes. In the following more complete report we shall especially analyze the relation between various sets of general and local effects of the injection of colloidal copper and casein, and the effect of these substances on the tumors. We shall compare the actions of solutions of colloidal copper with those of casein, and the effect of these substances in patients and in animals inoculated with carcinoma.

Our investigations were the outcome of preceding studies on the action of various sets of substances on animal tumors.² We wish here only to refer to a few of our results. We found that various sets of substances, as colloidal metals, certain protein substances and herudin, cause an inhibition or retardation, and in some cases a retrogression, of a certain number of tumors. Through a combination of several substances the effect of a single substance could be much increased. The efficacy of these substances depended especially on the age of the tumors, very young tumors being much more resistant to an inhibiting effect. Of special interest seemed to us the proof that repeated injections of these substances call forth in the injected animals processes of reaction against the injected substance.

These reactions have a double origin, being dependent on changes taking place (1) in the organism of the injected animal, and (2) in

* Submitted for publication Nov. 6, 1914.

1. Interstate Med. Jour., 1912, xix, No. 12; 1913, xx, Nos. 1 and 5; Jour. Am. Med. Assn., 1913, lx, 1857.

2. Loeb, Leo, and Fleisher, M. S.: Jour. Am. Med. Assn., 1913, lx, 1857; Fleisher, M. S., and Loeb, Leo: Jour. Exper. Med., 1914, xx, No. 5.

the tumor cells themselves. Thus an immunity of double origin becomes established. The immunity dependent on changes in the tumor cells can be transmitted to successive generations of tumor cells. The immunity thus established tends to prevent the continued effect of the various substances and to make it transitory. The immunity is a specific one; animals and tumors immunized against colloidal copper are immune against colloidal copper, but not against herudin and vice versa.³

We had intended to limit our work entirely to animal tumors, being doubtful as to whether animal experiments had advanced sufficiently to permit an extension to the field of human cancer, and it was only at the urgent request of physicians that we undertook our work on patients. While in the course of this work we observed marked improvement in the case of some patients, we stated from the beginning that our work was of an entirely experimental character, and we warned against its use in general practice, and very soon afterward we expressed the opinion that even in the most favorable cases a cure could not be expected through this kind of treatment.

While we thus rated the significance of these experiments from the point of view of direct applicability in the treatment of cancer as not very high, we believe that from the point of view of theoretical interest our observations make a more detailed publication advisable.

2. METHOD OF PREPARATION OF THE SOLUTION OF COLLOIDAL COPPER AND OF CASEIN AND TECHNIC OF INJECTION

For the preparation of colloidal copper we employed Bredig's method, at first, however, making use of an alternating current. Later we used a pulsating direct current obtained by means of a mercury arc rectifier. This passes through twenty-three large lamps of 32-candle power and five small lamps of 16-candle power; the wires terminate in copper electrodes 4 mm. in diameter. These are inserted into a beaker containing 1,500 to 2,000 c.c. of water, twice distilled. The water is first boiled to expel air and used after it has cooled. We used a current of 60 volts and from 16 to 18 ampères. The two electrodes are first brought into contact with each other and then gradually separated so that a spark is drawn out. When the passing of the spark stops, it is necessary to touch the wires again, separating them afterward gradually. This must be repeated again and again. We find it very convenient to attach one wire to an electric bell which keeps oscillating and drawing out sparks continuously. It is best to steam the beakers before using them the first time.

3. The possibility of an immunity against the action of the injected substances acquired through a relatively limited number of injections had been foreseen at an early stage of our work, and determined to a great extent the plan of our experiments. The same possibility we had in mind when we undertook our experiments on human cases and I expressed repeatedly in the beginning of our work the opinion that processes of immunization might prevent a continued efficiency of substances even in those cases which at first seemed to be beneficially influenced; I warned, on the basis of these considerations, against drawing definite conclusions as to the effect of these substances.—*Loeb*.

The copper wires must be cleaned each time with sandpaper before they are ready for use.

Preparation of Various Casein Solutions.—We used different casein preparations, purified as well as non-purified preparations. Into some casein solutions sulphur was introduced, with a view of possibly increasing the efficiency of the preparation. The effects of the various solutions were, in the main, due to the presence of the casein. Solutions prepared with commercial (impure) casein showed approximately the same effects as solutions prepared with purified casein. Addition of flowers of sulphur did not essentially modify the character of the solution. Solutions, however, into which sulphur had been introduced in the form of hydrogen sulphid (Solution 4 and Solutions 4, 16 and 13) were often more poisonous; it is probable that in such cases small quantities of hydrogen sulphid were left in the solution and caused some of the complications which were occasionally observed. The majority of the solutions contained about 1 to 1½ per cent. casein.

Technic of Injection.—The technic used in giving intravenous injections of colloidal copper and casein is about the same as that used for injecting salvarsan, except that in the case of colloidal copper and casein it is unnecessary to use normal salt solution either in the beginning or at the end of the injection. A No. 24 Burroughs-Wellcome needle was generally used in our work. We used a pressure apparatus⁴ which eliminated all waste of time and enabled the operator to inject as many as twenty-three patients in six hours, two patients being injected at the same time. This apparatus consisted of a reservoir containing the solution to be injected, two dosage containers and a drum for compressed air. The amount of pressure was regulated by a mercury manometer. The fluid in the dosage containers was kept at a constant temperature by an electric stove regulated by a thermostat, which kept the temperature constant within one-fifteenth of a degree. With this apparatus we were able to keep temperature and pressure constant. The pressure we used depended on the way the patient stood the injection, on the size of the veins and on the amount of fluid to be injected, and was regulated accordingly.

3. EFFECT OF THE INJECTIONS OF COLLOIDAL COPPER AND OF CASEIN ON THE VEINS

It is of practical as well as theoretical interest to analyze the effect of the injections of casein and colloidal copper on the walls of the veins with which the injected fluid came into contact after injection.

We consider especially here the pathological changes taking place in the injected veins. The following facts concerning these changes may prove of interest:

1. Injections of casein solutions were tolerated by almost all patients without any resulting changes in the veins. In two cases, however, even the casein had an injurious effect on the veins; both of these cases were in old men, in whom also the colloidal copper had a very marked effect on the veins. In contradistinction to casein, the injection of colloidal copper caused some changes—sometimes very slight and transitory, sometimes very marked and permanent—in the majority of patients. We may therefore conclude that colloidal copper,

4. This apparatus was devised by Dr. W. O. Sweek and made by F. F. Dietz.

and probably also other colloidal metals, cause, in contact with the wall of the veins, pathological changes.

2. In general we can say that the more intimate the contact of the colloidal particles of metal with the wall of the vein, the more marked were the changes.

3. The frequency with which a vein could in the same area be injected with the colloidal copper differed very much in different individuals. In general we can state that frequent repetition of the injections, therefore of the action of colloidal copper, leads to changes, even in cases in which a single injection is without apparent effect. The time required for an affected vein to enable it to return again to its approximately normal condition differed in the case of different individuals.

We may assume that in every case some changes take place in the wall of the vein as a result of the contact with the colloidal copper. In some cases, however, they are very marked, while in others they are very slight. But even in the latter frequent repetition of the injections at a time when the vein had not yet resumed its normal condition leads to a summation of the pathological changes.

4. The changes themselves consist evidently in an injury to the endothelial cells, which makes the latter more permeable to fluid constituents of the blood. Fluid parts of the blood are therefore liable to infiltrate the vessel-wall and the neighboring tissue and make the vein hard and swollen. It is also probable that some of the colloidal particles of copper in some cases enter and irritate the surrounding tissue and then cause a dilatation of the vasa vasorum, thus producing redness of the area surrounding the vessel-wall. Occasionally, the permeability of the vessel-wall may become so markedly increased that edema of a part of the injected extremity follows. Colloidal copper acts, therefore, in this case similarly to certain substances which are supposed to cause, after intravenous injection, edema as a result of injury of the endothelium (as for instance arsenic preparations).

5. It is of great interest that the reaction of the vascular endothelium to injurious influences seems to depend on a sensitiveness variable in different individuals. Even if we allow for differences in the size of the veins, in the rapidity of the flow of the solution in the vessels, in age and general condition of health of the person, there remains usually a factor which points to individual differences. On the whole the veins of strong men are usually more resistant to the injurious effect of the colloidal copper than the veins of emaciated and weak patients; but we found strong men with large veins whose veins proved very sensitive toward the contact with colloidal copper, and, while weak and emaciated women have usually less resistant veins

than strong young women, some old and emaciated patients had resistant veins. In addition, it is probable that a kind of work leading to marked development of the muscles of the arms tends to make the veins more resistant. Two persons whose veins had been most resistant to the action of colloidal copper had both been blacksmiths.

4. GENERAL EFFECTS OF THE INJECTIONS OF COLLOIDAL COPPER AND CASEIN

I. QUANTITIES INJECTED

We started usually with relatively small doses of colloidal copper and of casein and gradually increased the quantities injected, using the general reactions following the injection as an indicator of the rate at which the dose could be increased. The first dose was usually 100 or 150 c.c. of colloidal copper and in the majority of cases it was gradually raised to 400 c.c.; in some cases much larger doses were injected. The time when the dose of 400 c.c. was reached varied in different cases. If the dose was rapidly advanced it could be reached at the time of the fifth injection; in other cases it was reached between the eighth and twelfth injections. The number of injections given in different cases varied in the majority of cases between twenty-five and seventy-three. In some cases only a total of from thirteen to sixteen injections was given. Usually four or five, in one case three or four, injections were given each week.

In most cases in which casein was used the injections followed a preceding series of injections of colloidal copper; but between these casein injections there was usually interspersed a smaller or larger number of injections of colloidal copper; sometimes the series of colloidal copper injections was directly followed by a casein series, and only in the later period of the casein injections were injections of colloidal copper again interspersed among the casein injections. In some cases the initial series of copper injections consisted of more than twenty-five, in other cases of only five injections; the number of copper injections interspersed with those of casein also varied in different cases. In one case there was first given a series of casein injections and later some copper injections were given alternately with the casein injections. The amount of casein given in each injection varied much in different cases. Especially, however, in the later period in our work we chose very small initial doses, somewhere between 2 and 5 c.c. In other cases, especially in the earlier period, as much as from 11 to 25 c.c. were chosen as the initial doses, and in some cases even larger initial doses had been given. While some persons could stand these latter quantities comparatively well, in others an extremely strong reaction followed. Gradually in the course of

treatment the doses were increased, in some cases to a maximum of 25 c.c., in others to 50 c.c.; in still others to 90 c.c., and in one patient as much as 155 c.c. were given in one injection. This same patient also received twice at the same injection 200 c.c. colloidal copper immediately followed by 50 c.c. of casein. The number of casein injections given to the individual patients varied very much. Some patients received as many as 48, 46, 36, 32 and 31 injections, others received only between 15 and 21, and still others only a few injections. In most cases two or three injections were given in the course of a week; occasionally there were intervals up to nineteen days between two injections, and in some patients there were, during a certain period, injections given on successive days.

II. THE EFFECT OF INJECTIONS OF COLLOIDAL COPPER ON THE TEMPERATURE CURVE

Intravenous injections of colloidal copper were usually followed by a rise in temperature. This rise began within the first hour and reached its maximum several hours after the injection. In some cases in which a large quantity of the solution had been injected, the maximum rise was reached from five to seven hours after the injection; the temperature usually became normal again on the day of the injection; but on several occasions the temperature was still abnormal on the day following an injection, without a new injection having been given. Thus in the case of a strong man, following the twenty-third injection the temperature rose on the day of the injection to 100 F., and on the following day the temperature was still 99. In this case no complications (as, for instance, an infection) were present which could have explained the rise on the second day. In other cases there was, however, especially in the later stages of the disease, sometimes an infectious process present as a complication which in itself caused a rise in temperature, and to which the rise in temperature caused by the injection was added. In such cases we found a rise in temperature even on days on which no injection had been given.

An analysis of the various cases shows the following factors to be of importance in determining the extent in the rise of temperature observed:

1. The quantity of fluid injected. On the whole we can say that the larger the quantity injected the greater the rise.
2. This factor is, however, complicated by a second factor which, during the period of the later injections, tends to counteract the gradual rise in temperature which should be expected in accordance with the gradual increase in the doses; namely, an immunity which is gradually established as the result of the injections; we shall consider this factor

separately later on. The gradual production of an immunity during the course of the injections makes it necessary to compare in the different cases the effect of the first injections on the temperature. If we do this we notice then that

3. There are individual differences in different patients as far as the rise in temperature is concerned. In some cases the temperature after the first few injections rose hardly at all or not higher than a little above 99 F., and only rarely to 100. This effect we found especially, but not exclusively, in relatively strong persons; in a few rather old and not very strong patients the general reactions were also relatively slight. In a considerable number of cases the rise varied approximately between 99 and 100 F. This class includes a number of weak as well as of strong persons. In a third class, not quite so numerous as the others, the rise varied between 100.5 and 102. This class included mostly weak persons. We find, therefore, as the third factor, individual characteristics, among which the physical strength of a patient seems to be of great importance.

4. In regard to some accidental factors we cannot speak with the same degree of certainty. It seems, however, that some variations in the temperature of the injected fluid (too low a temperature causing higher fever) variations in the size and number of colloidal particles in a volume unit of fluid and perhaps the rapidity of injection had, in some cases, some influence on the degree of fever. We also noticed that if on two successive days the same amount of solution was given, there was occasionally a more marked rise on the second day. We have in such cases possibly to deal with a summation of effects, which, however, cannot consist in a summation of the fever curves, the temperature being usually normal on the day following an injection; but it may consist in a summation of changes somewhere in the body indirectly connected with the rise in temperature. Bacteriological examination of the solutions of colloidal copper proved them to be sterile. The rise in temperature following the injections can therefore not have been due to admixture of bacteria.

III. IMMUNITY ACQUIRED AGAINST THE EFFECT OF COLLOIDAL COPPER ON THE TEMPERATURE

The rise in temperature which followed the injections of colloidal copper became generally less, the larger the number of injections given; this applies to all classes of persons, as well to those in whom the reaction had at first been very marked, as also to those with a reaction of medium strength in the beginning, and to those in whom from the beginning the reaction had been weak. While in the first

two classes the acquired immunity could be easily demonstrated, inasmuch as notwithstanding the larger doses given at later periods the rise in temperature became less, in the last class the establishment of an immunity could be assumed on the strength of the fact that the larger doses given later did not cause a more marked, or even caused a somewhat weaker, reaction than the first smaller doses. In no case was the immunity absolute. There were usually some injections which caused, again, a more marked rise in temperature. In some cases in which at first the reaction had been very marked, it was almost entirely absent in the later periods, while in other cases the difference between the first and later reactions, although present, was not so marked; in these cases the transition from the not immunized to the immunized state was more gradual. In a few cases no definite immunity could be shown to exist. While in some cases this was due to the appearance of complicating processes tending in themselves to raise the temperature, in a few exceptional cases no immunity was apparently produced. In some cases partial immunity became noticeable as early as after the fourth or fifth injection; in others it required from ten to twelve; in still others from fifteen to sixteen injections, before the immunity became marked. After the first sixteen injections the immunity became usually especially marked.

The immunity produced against the general effects of colloidal copper is not specific. It can also be produced through preliminary injections of solutions of casein which on their part cause a marked rise in temperature. We found that in patients in whom, after a series of injections of colloidal copper, a series of injections of casein was given, and in whom after a number of casein injections again a large dose of colloidal copper was injected, the injection of colloidal copper was either followed by no fever reaction at all or by a much slighter reaction than those observed previous to the injections of casein. It appears even probable that many conditions giving rise to a transitory elevation of temperature may thereby lessen the general effects of colloidal copper. In such cases we may have to deal with a lessened excitability of certain nervous mechanisms as a result of previous stimulations.

IV. SOME OTHER EFFECTS OF INTRAVENOUS INJECTIONS OF COLLOIDAL COPPER

Besides the rise in temperature, the most common effect following the injections of colloidal copper was a chill; in most cases beginning about thirty minutes (twenty to sixty minutes in individual cases) after the injection. It lasted usually about half an hour. The presence and intensity of the chill depended, in the same individual, on the

height in the rise of the temperature following the injection. There was a correspondence in the same individual between the severity of the chill and the temperature curve. There was, however, a great difference between different individuals in the liability of a chill to follow the injection. In one patient, a strong man, in whom the temperature showed only slight rises after the injections, there was usually a marked chill present; also at times when the rise in temperature was almost absent. In another patient, an old man, in whom also the rise in temperature was usually slight, a chill was only once observed, viz., after the twenty-fourth injection, when the temperature rose to 100. In typical cases a slight chill seemed to correspond to a rise in temperature to about 101, while a severe chill followed a rise to 102 or higher. In other persons, however, there was a slight chill when the temperature went up to 100, and a severe chill when the temperature went up to 101 or higher; this was the case, for instance, in a girl 16 years old. There were occasionally some other symptoms present; but in most cases they were only exceptionally noticed and found only on occasions when the temperature rose somewhat higher than usual. Such isolated occurrences were: an attack of dizziness, perspiration and symptoms of syncope, pain in head and back, abdominal cramps and vomiting. Other symptoms were on several occasions observed in an old man of strong build. Here the injections were followed by weakness, irregular pulse and vomiting. In an otherwise strong young girl the injections were regularly followed by headache and pain in the arms. When the temperature remained below 100 there was usually no chill, but slight headache and pain in one or both arms were observed.

V. THE EFFECT OF INJECTIONS OF CASEIN ON THE TEMPERATURE CURVE

During the first period the temperature following an intravenous injection of casein was higher than after the copper injection during the corresponding period. This holds good even in cases in which small doses (from 2 to 4 c.c. of the solution) were used during the first injections. In the majority of cases the maximal temperature after the first three or four injections varied between 101 and 104. In some cases it was still higher; in some resistant persons, especially persons of strong build, it did not reach 101. The fever curve after these injections had a steeper course than after injections of colloidal copper, at least in those cases in which large quantities of colloidal copper were injected; the maximum temperature was usually reached earlier than

after injections of colloidal copper, viz., between one and one-half and three hours after the injection; after five or six hours the temperature became usually normal or almost normal again. In some cases, however, in which with the first injections relatively large doses were given, or in which the patient was very sensitive to the casein, the temperature remained high even for considerably longer than a day. In a patient, e. g., in whom, after the first injection the temperature rose on the first day to 105.4, the temperature returned to normal only on the twelfth day after the injection. There seemed to be an individual difference in different individuals, as to the time required in which, after about the same maximum had been reached within a few hours, the temperature returns to the normal point. We must assume that in those cases in which the temperature remains high during a long period, unchanged or only slightly changed casein is circulating in the blood, while in those cases in which smaller doses were given or otherwise the body was normally able to split or eliminate the casein more rapidly, the temperature becomes more rapidly normal. We see accordingly that a long-continued rise in temperature is especially noticeable following one of the first three injections, while later, when a certain immunity has been reached, the return to the normal point is usually more rapid, although the doses given may be much higher than at first. In one person, in whom the temperature remained high during several days, and in whom we gave special attention to this point, the temperature during the afternoon was found to be from 0.2 to 0.6 higher than in the morning.

On the whole the same factors which determined the rise in temperature after injections of colloidal copper are also of importance in the case of casein. The immunity acquired in the course of these injections we shall discuss separately. The size of the doses given determines to a great extent the rise of the temperature. But there remain, besides, individual factors. If we compare several persons who receive in the first injection approximately the same doses, the severity of the reaction is not the same. Thus in one person in whom the injections of colloidal copper caused only very little rise in temperature, casein solutions caused also relatively slight changes in temperature. Here also some strongly built patients seem to be more resistant than weaker persons. Larger initial doses which one patient tolerates with only moderately severe reaction, may cause in another person reactions of a very great severity. If 2 c.c. were given as the initial dose and during the first three or four injections the dose was not increased more than 1 or 2 c.c. each time, only relatively slight or moderately severe reactions were observed.

VI. IMMUNITY ACQUIRED AGAINST THE EFFECTS OF CASEIN ON
THE TEMPERATURE

Just as after injections of colloidal copper, an immunity against the effects of casein was produced through repeated injections. In the typical cases we can distinguish three periods in the process of immunization. The first definite signs of immunity became noticeable at the time of the fourth injection about eight days after the beginning of the injections. Then there followed an intermediate period lasting from the fourth to the twelfth or twenty-second injection, during which, notwithstanding the larger doses of casein, the temperature was 1° or 2° lower than in the beginning. This period was followed by a third period comprising the later injections in which, notwithstanding the still higher doses given, the rise in temperature was still more reduced, and in some cases not rarely remained normal after the injections, while occasionally there was a slight rise to 99 or 100, which in a few cases might have been greater. In other cases, however, in which the doses were increased more rapidly, the early onset of the immunity after the first three injections was not so clear. In a strong man, for instance, immunity became clear only after the first twenty injections. Notwithstanding the higher doses given, the temperature was now, on the average, less than after the former injections. In a strong girl 16 years old in whom the fever reaction following the injection was usually very marked, a definite immunity was established only after about thirty-six injections, three months after the beginning of the administration of casein. Immunity becomes established not only in strong, but also in weak persons in whom metastases are present in internal organs at the time of the treatment. In our cases we had of course to deal with the complication consisting in the gradual increase in the doses of casein given. It was therefore possible that in a certain case the immunity existed at a time when the temperature reaction did not decrease in the course of the successive injections, but in such cases the immunity became apparent through the lack of increase in fever in successive injections, notwithstanding the increase in the doses given; the immunity established was in no case absolute, but only partial.

In some cases there was an interval varying between ten and nineteen days between two successive injections. It was of interest to determine whether the injections following the interval would be accompanied by signs of an anaphylactic reaction. While on two occasions it can be definitely stated that such a reaction did not occur, the reaction being not more marked after the injection following the interval than after the preceding injection, on two other occasions the injection following the interval caused relatively severe symptoms.

In those cases in which an anaphylactic reaction can be definitely excluded, we may assume that the quantity of casein given in the course of the preceding injections had been too great to make possible the establishment of anaphylaxis within a relatively short interval of time.

While as we saw, previous injections of casein cause a marked decrease in the general effects following the injections of colloidal copper, the converse condition does not hold good: Preliminary injections of colloidal copper do not protect against the general effects of casein. In this connection we must remember that injections of casein caused very much more marked general reactions than colloidal copper.

If we compare the curve of immunization produced through injections of colloidal copper with the curve resulting from injections of casein, we see on the whole a definite parallelism as to the time when the immunization first becomes apparent and when it becomes more marked.

VII. OTHER EFFECTS FOLLOWING INTRAVENOUS INJECTIONS OF CASEIN SOLUTIONS

Other symptoms besides temperature were more severe after casein than after colloidal copper injections. A chill beginning from thirty to forty-five minutes after the injection and lasting about half an hour was a very common symptom after use of casein as well as of colloidal copper. In the same individual there was on the whole a parallelism between the severity of the chill and the height of the rise in temperature following the injection; frequently a temperature below 101 F. was preceded by a relatively slight, a temperature of 102 or more by a severe, chill. But in the same individual the correspondence between height of rise in temperature and severity of chill was not complete. We find here again a similar difference between individuals as we found in the case of colloidal copper. Some persons were inclined to have a chill after injection of colloidal copper as well as of casein, even in the case of only a slight rise in temperature; in other persons after administration of copper, as well as of casein, a higher temperature was required than in others to produce a chill. When there was a marked rise in temperature, perspiration was not infrequently observed, and after the maximum of the fever had been reached, pain in the region of the stomach and vomiting occurred in a number of cases. These latter symptoms followed much more frequently injections of casein than of colloidal copper. It seems probable that the injection of casein causes contraction of the stomach. A very common symptom after injections of casein was pain in the back; it started often before the injection was finished. This symptom appeared more frequently

in some patients than in others. In some severe cases there was pain over all parts of the body, but sometimes especially localized around the tumor. Thus in a patient with a lesion in the right humerus the arm was affected; in others the face, if the lesion was in the face. In a patient with metastases in the liver, after an injection of a relatively large dose of casein, severe pain in the liver region appeared. In some cases pain around the seat of the lesion was present even if the rise in temperature was very slight. In a few cases this localized pain, appearing about one hour after an injection, was the most persistent symptom next to the rise in temperature. After large doses followed by marked general effects, pain around the tumor may be present one or several days after the injection. In a few cases injections of casein were followed by cardiac and respiratory disturbances: cyanosis, weak irregular pulse and rapid, shallow respiration; in such cases the temperature was usually high, for instance 104.6 in one case. While such attacks were, on the whole, exceptional occurrences, in one or two patients irregular pulse following the injections was a more frequent symptom. It is possible that some heart lesion existed in such patients.

There remain a few exceptional symptoms to be mentioned, viz., herpes labialis, which followed the injection of casein in two cases on occasions when a marked rise in temperature was present. In one patient the twenty-first injection was followed by an erythematous eruption of the skin. On the whole, those casein preparations which caused a more marked rise in temperature caused also more severe other symptoms. With increasing immunity the other symptoms gradually disappeared simultaneously with the fever. In a few cases one of the first three injections was, as mentioned above, followed by very severe symptoms. In these cases, too large doses had been given.⁵ It concerned four patients who received the injection at about the same time. The following case may be cited in detail:

CASE 1 (No. 3614).—Multiple carcinoma of face and neck. The first injection of 15 c.c. casein was followed by slight symptoms. At the time of the second injection almost 30 c.c. were given. During the injection there was severe pain in the back. For a period of one-half hour there was, every five minutes, a convulsion lasting two or three minutes; the face was red, breathing irregular, pulse rapid. Thirty minutes after the injection there was a severe chill lasting from twenty-five to thirty minutes, followed by a rise in temperature to 106 F., reached five and one-half hours after the injection; delirium and anuria were present, and lasted twenty-four hours. The following twelve days the patient was unable to eat, he lost weight and felt weak. After two weeks he began again to gain in weight and was normal at the end of six weeks. We shall have occasion later to refer to the effects of these injections on the tumor.

5. This was an accidental happening during an unavoidable absence of one of us.

5. EFFECTS OF INTRAVENOUS INJECTIONS OF COLLOIDAL COPPER AND OF CASEIN ON THE BLOOD

1. EFFECT OF THE INJECTIONS OF COLLOIDAL COPPER ON THE NUMBER OF ERYTHROCYTES

We can divide the patients in four categories:

1. In some patients there was a decrease in the number of erythrocytes caused by the injections. This decrease was, however, not very great. Thus, in one well-built patient the number of erythrocytes diminished in the course of ten injections from 5,100,000 to 4,400,000. This decrease is relatively slight. In some cases it is confined to the first period of injections, and in the course of the later injections the number may again increase. In other cases there is a decrease also during the later injections, but after completion of the series of injections a recovery takes place.

2. In some patients in whom anemia was present from the beginning, the anemia progressed during the course of injections, but the decrease in erythrocytes was not more marked than could be expected as a result of the disease. These were patients in whom there were large suppurating or putrid, ulcerated surfaces.

3. In some other cases there was no noticeable decrease, and this applied mostly to less advanced cases, but it was also found in a patient who had at the beginning of the injections 2,100,000, and after a series of fifteen injections 2,200,000 erythrocytes.

4. In one case we found a distinct increase during the course of injections. This was a patient with a carcinoma affecting the orbital cavity and its environment. At the beginning there were 3,700,000, one and one-half months later 4,200,000 and two and one-half months later 4,900,000; nine days after the last (seventy-third) injection, more than three months after the beginning, 5,200,000; three and one-half months after the last injection 6,420,000; six and one-half months after the last injection 4,300,000 erythrocytes. This was the case of a strong man who received very large quantities of the solution at each injection. The maximum was 1,200 c.c.

In some cases we made a count directly before an injection as well as a few hours later. In such cases we found usually a very slight decrease in the number of erythrocytes after the injections.

We may therefore conclude that after the injections of colloidal copper a certain number of erythrocytes are destroyed; that in some cases the reparatory changes which take place suffice to replace the lost red blood corpuscles. Such reparatory processes may occur even in very anemic persons in whom a destruction of erythrocytes took place as the result of other injurious influences, which latter loss the blood-

forming organs were not able to repair. In some cases the reparatory processes are not quite strong enough to keep the number of erythrocytes at the normal level. In such cases the reparatory processes may, however, after cessation of the injections, be strong enough to replace the lost erythrocytes.

II. EFFECTS OF INTRAVENOUS INJECTIONS OF CASEIN ON THE NUMBER OF ERYTHROCYTES

Injections of casein did not usually produce any noticeable decrease in the number of erythrocytes. While possibly in some cases a severe reaction following casein injections may have caused a slight decrease, there was usually no marked difference in the number of erythrocytes at the beginning and at the end of the casein injections. In one case there was even a gain during the period of immunity against the general effects of casein injections. In other cases an increase began to take place after the course of injections had been completed.

In cases in which the disease itself leads to an increasing destruction of erythrocytes, injections of casein cannot prevent the decrease. Intravenous injections of casein have therefore no marked influence on the number of erythrocytes; they neither diminish them very markedly nor do they prevent a decrease produced by other conditions.

III. EFFECT OF THE INTRAVENOUS INJECTIONS OF SOLUTIONS OF COLLOIDAL COPPER AND OF CASEIN ON THE LEUKOCYTES

A complete study of the effect of these solutions on the leukocytes, including a detailed determination of the number of the various leukocytes following injections in each patient, at different periods of the treatment, could not be carried out. In a few cases, however, the leukocytes were studied at different times following an injection. In most cases only one examination was made following an injection and only after certain injections. We may, however, state that a leukocytosis often follows injections of colloidal copper as well as of casein, and that the leukocytosis following injections of casein is usually more marked than the leukocytosis following the injections of colloidal copper. This corresponds with the higher fever which usually follows injections of casein. The maximum of the leukocytosis seems to be reached somewhere between two and five hours after the injections; eight hours after the injections the number of leukocytes is often again normal. In some cases, however, when the general reactions following the injections of casein have been very severe, and fever lasts longer than twenty-four hours, the leukocyte count may still be high twenty-four hours after the injection. Even many injections of either casein or colloidal copper did not produce a complete immunity against the

effect of these substances as far as the effect on the leukocytes is concerned.

The increase in leukocytes was in the main due to an increase in the number of neutrophil polynuclear leukocytes. It is possible that at the same time there existed also an absolute increase in the number of lymphocytes. In some cases in which there existed a relative increase in the lymphocytes, injections of casein produced only a very slight, if any, increase in the total number of leukocytes, but principally a change in the proportion of different kinds of leukocytes. Thus, in the repeatedly mentioned case of a 16-year-old girl there was, three and one-half months after the beginning of the injections, preceding an injection of casein, 9,800 leukocytes. Of these there were 48 per cent. polynuclear neutrophils, and from 50 to 52 per cent. lymphocytes. Three hours after the injection of casein the number of leukocytes had only slightly increased, namely, to 11,000, but the polynuclears had increased to 74 per cent. and the lymphocytes had decreased 50 per cent., namely, to 25 per cent.

IV. A RELATIVE INCREASE IN THE NUMBER OF LYMPHOCYTES PRODUCED THROUGH LONG-CONTINUED INJECTIONS OF EITHER COLLOIDAL COPPER OR CASEIN

The changes in the number of leukocytes mentioned above represent merely transitory changes. It is now of special interest that a large number of injections of colloidal copper or casein, given through a considerable period of time, have, in addition, an influence on the relative number of the various leukocytes, and this influence persists over a long period of time. While the transitory effect consists in an absolute increase in the number of polynuclear neutrophils, the long-continued effect consists in the opposite change, namely, a relative increase in lymphocytes, especially of the small lymphocytes, and a relative decrease of the polynuclear neutrophils. We have observed these changes in all those cases in which the blood examinations were made at intervals through relatively long periods of time. The change became usually distinct about two or two and one-half months after the beginning of the treatment, reached a maximum approximately from three to six or eight months after the beginning and then commenced slowly to decline. This condition lasted, therefore, much longer than the period of injections. It is observed in the following cases:

CASE 2 (No. 3641).—White man, aged 34; multiple carcinoma of the skin. The beginning of the change was noticed somewhat more than two months after the commencement of the treatment and during the period of casein injections. While previously the number of polynuclears had been above 77 per cent., and of lymphocytes 20 per cent., or less, somewhat more than sixty days

after the beginning of the treatment there were 67 per cent. polynuclear neutrophil leukocytes, 27 per cent. small, and 6 per cent. large lymphocytes. About five months after the beginning of the injections of colloidal copper, and three and one-half months after the beginning of the injections of casein, there were 48 per cent. polynuclear leukocytes, 48 per cent. small and 4 per cent. large lymphocytes; the number of leukocytes was increased to 10,800. For the next two or three months the count remained approximately the same, although the total number of leukocytes returned to normal. This change was still present, but perhaps slightly less marked eight and one-half months after the beginning of the treatment and almost two months after the last injection. At that time there were present at two counts made at two days' intervals: polynucleurs varying between 48 per cent. and 60 per cent., small lymphocytes varying between 32 per cent. and 48 per cent.; 3 per cent. large lymphocytes, transitional leukocytes varying between 1 and 3 per cent. and eosinophils varying between 2 and 4 per cent. At a count made fourteen and one-half months after the last injection (Aug. 31, 1914) examination of the blood showed the following condition:

Erythrocytes	4,720,000
White blood cells	15,600
Polynuclear neutrophil leukocytes.....	56 per cent.
Large and small lymphocytes.....	41 per cent.
Large mononuclear cells.....	1 per cent.
Eosinophils	2 per cent.

We see, therefore, that this change is not of a transitory character, but persists for a long period of time.

CASE 3 (No. 1436).—Woman, aged 69; carcinoma of face, affecting the ear. Two months after the beginning of the injection there were 68 per cent. polynuclear neutrophil leukocytes, 30 per cent. lymphocytes and 2 per cent. eosinophils present. Two and one-half months after the beginning of the treatment there were 57 per cent. polynucleurs and 5 per cent. eosinophils. Three months and nine days after beginning of the treatment there were 57 per cent. polynucleurs, 40 per cent. lymphocytes and 2 per cent. eosinophils. Five months after the beginning and thirty-nine days after the end of the treatment there were 48 per cent. polynucleurs, 49 per cent. lymphocytes and 3 per cent. eosinophils. One month later the polynucleurs had decreased to 45 per cent. and the lymphocytes had increased to 48 per cent.; there were 4 per cent. eosinophils. Nine months after the beginning of the treatment and five months after the completion of the treatment, the lymphocytes had again decreased to 40 per cent., the polynucleurs had increased to 52 per cent., and the eosinophils to 2 per cent. Twelve or thirteen months after the beginning and eight or nine months after the completion of the treatment, there was a further rise in polynucleurs, whose number varied between 58 per cent. and 68 per cent.; there were between 31 per cent. and 41 per cent. lymphocytes (about 16 per cent. of which were large lymphocytes). There were also 1 per cent. eosinophils. Similar observations which do not need to be given in detail were made in the following cases:

CASE 4 (No. 1476).—Man, aged 59. Carcinoma of the cheek.

CASE 5 (No. 1504).—Man, aged 56. Carcinoma of the eyelids extending to the eye.

CASE 6 (No. 1502).—Man, aged 57. Carcinoma affecting the skin in the neighborhood of the eye.

CASE 7.—R. M., girl, aged 16. Swelling in the humerus of the right arm, diagnosed as sarcoma.

In Cases 3 (1436) and 6 (1502) we can attribute the change to the effect of colloidal copper. In Case 6 (1502) no casein had been given. In Case 7 only a few injections of colloidal copper had been given,

and the changes were in all probability due to casein. In the other cases a larger number of injections of both casein and colloidal copper had been given. This relative increase in lymphocytes is at certain times accompanied by an increase in the total number of leukocytes; at other times the latter is absent. We see, furthermore, that old and young, strong and weak persons, can show this change. We have to distinguish such cases from others in which already before the beginning of the treatment a relative lymphocytosis is present.

In some cases it seems that the first changes in this direction were observed from five to eight weeks after the beginning of the treatment; but inasmuch as no continued examinations of the blood were made in these cases, no definite statements concerning the point can be made.

As to the significance of these changes, it is probable that they represent a reaction of the organism toward all kinds of substances administered during a long period of time which cause a rise in temperature and a transitory increase in polynuclear neutrophil leukocytes. But whether this reaction consists in a mere change in the distribution of the various kinds of leukocytes in the superficial and in the deeper blood vessels, or whether we have to deal with an actual new formation of lymphocytes, cannot be decided with certainty at present, although the latter alternative seems to be more probable. It has been observed by Baeslack⁶ that there is an increased lymphocytosis present in cancerous animals during the period of retrogression of a cancer. We can exclude with certainty in our cases any relation of the lymphocytosis to retrogressive changes, which latter took place in some cases long before the onset of the lymphocytosis and in other cases was lacking notwithstanding the lymphocytosis.

6. Report on meeting of American Association for Cancer Research, 1913, in *Ztschr. f. Krebsforsch.*, 1913, xii, 441. Baeslack mentions also two cases of human cancer (sarcoma of upper jaw and carcinoma of uterus) in which during a period of retrogression there was an increase in lymphocytes. It may be also mentioned that Harlan Shoemaker (*New York Med. Jour.*, 1913, xlviii, 2-18) states that in the treatment of pellagra, after a first period of injections of colloidal copper, in which the polynuclears increase in the period directly following the injections, there is a later period during which the small mononuclear blood cells are increased, and still later the large mononuclear cells appear. This is an interesting observation. We believe, however, that we must distinguish between two phenomena, viz: 1. The temporary increase of polynuclear leukocytes following each injection of colloidal metal. Such a temporary reaction may still be present even at a later period, when the lymphocytes are already relatively and absolutely increased, and this increase in polynuclear leukocytes may superimpose itself on the lymphocytosis. 2. A later lymphocytosis, which in contradistinction to the increase in polynuclear leukocytes is not directly, but only indirectly, caused by the injections; it is a chronic condition lasting for a long period of time, after the injections have been omitted. It is not only produced through colloidal metals, but also through injections of casein and probably other substances causing a temporary increase in polynuclear leukocytes.

6. EFFECTS OF THE INTRAVENOUS INJECTIONS OF COLLOIDAL COPPER AND CASEIN ON THE TUMORS AND THEIR SURROUNDING TISSUES

We may divide the changes which we observed in two classes: (1) in those not directly representing healing processes, but processes more or less common to all tumors, and (2) changes representing a healing process, or the first stage of it, or a process, while not actually connected with healing, bringing some relief to the patient. A sharp line between these two kinds of effects cannot be drawn, and some might be just as appropriately classed with the one as with the other.

1. EFFECTS OF THE INTRAVENOUS INJECTIONS OF COLLOIDAL COPPER AND CASEIN ON THE TUMOR, NOT REPRESENTING HEALING PROCESSES

Besides the general effects which we described above, definite changes take place in the tumors and various tissues surrounding the tumors after the intravenous injections of colloidal copper and casein. *These changes might be characterized as a localized inflammation caused by substances introduced into the circulation at a place distant from the place of injections.* We have to deal with an experimentally produced inflammation. A localized effect is produced through an interference affecting the whole organism. The essential feature of the localized reaction is a hyperemia affecting the tumor and its neighborhood. It may not only affect the immediate neighborhood, but also extend somewhat further into the surrounding parts of the organism, and the extension is generally the greater, the more severe the reaction. For instance, if a lesion is situated at the lower lip and chin, the whole face may become swollen and the conjunctiva injected in the case of a severe reaction; and even the middle ear may show some effect. In open lesions the hyperemia may lead to small hemorrhages, which become noticeable in the form of hemorrhagic scabs over the ulcer or in a blood-stained secretion.

The hyperemia is followed by and is to a great extent the cause of the typical symptoms of inflammation, namely, swelling, redness, increased secretion and sensation of pain or allied sensations. The swelling following the injection can in some cases be seen soon after the injection, and can also be measured in favorable cases. Thus in a patient with a lesion affecting the humerus, the circumference of the arm would increase $\frac{1}{2}$ to 1 inch after an injection. Even after the fourteenth casein injection such an increase could be observed. This swelling takes place sometimes during the period of rise of temperature; it occurs, therefore, before the maximum of temperature has been reached. But it may also be present somewhat later. Thus,

swelling of the neighboring lymph-glands was present four hours after injection and had subsided the following morning. The increase in hyperemia leads in the case of superficial lesions to redness of the surrounding tissue, and sometimes to a bluish purple coloration.

Increased secretion becomes noticeable in ulcerated tumors after the first few injections; for instance, as early as after the second injection. It may follow copper as well as casein injections. Sometimes a clear serous fluid is secreted, but at other times the secreted material may appear purulent or putrid. Infection of the ulcer by organisms is present in such cases. The swelling following the injections is in all probability due to the increased secretion as well as to hyperemia. If the increased transudate cannot be eliminated through an ulcerating surface, it might collect and cause swelling, as, for instance, in a cancerous lymph-gland, or in a lymph-gland not yet itself the seat of a metastasis, but situated in the neighborhood of a tumor.

The hyperemia and increased transudate causes also probably the pain or burning or itching sensation following injections in and around the tumor. These sensations may also radiate into a zone further removed from the tumor. For instance, in a case with a lesion in the right humerus, the pain was often felt not only in the diseased right, but also in the healthy left arm. These sensations are at their height just as the swelling before the maximum temperature has been reached. It may start three quarters of an hour or an hour after injection, and may have subsided within three hours. Local pain may be the most persistent symptom following the injections, more persistent than fever; such was the case, for instance, in the patient with a lesion of the humerus. Pain may be present after an injection of copper as well as of casein. If fever persists for several days after an injection, pain may also be felt for a few days after injection. Even with a slight fever, pain may be severe. Colloidal copper and casein produce essentially the same "inflammatory" reactions, only after casein the reactions were usually more severe; there was more pain, swelling and secretion. The relative intensity of the reactions following colloidal copper and casein varies in different cases. In some cases the reactions -- general as well as local -- are almost absent after colloidal copper, while they are marked after casein; in other cases they are present after colloidal copper, but stronger after casein.

There exists a definite relation between general and local reactions; in most cases both follow a parallel course. Usually a severe general reaction is accompanied by severe local reactions. For instance, in a certain case in which the general reaction following a certain number of injections was slight, the local reactions were also slight. Then there followed at a later injection a severe general reaction and the

local reaction also was much more marked than previously. In other cases the general reactions following injections of colloidal copper were entirely or almost lacking; in such cases the local reactions were also entirely or almost entirely absent. Furthermore, those preparations of casein which produce the most severe general reactions call forth equally marked local reactions. It may, however, occasionally occur that with relatively slight fever (99.8 F.) at one of the later injections, the local reactions (consisting, for example, in swelling of the face in a patient with a carcinoma of the lower lip) may be very severe. We may therefore conclude that the conditions determining the severity of the local and general reactions are the same; that there may, however, in some cases, in addition to these common conditions, exist some special conditions influencing separately either set of reactions.

We can more or less distinctly distinguish in most cases three periods as far as the character of the local reaction is concerned. In the first period all the inflammatory signs are most pronounced; increased redness and swelling around the tumor may be the first sign; a little later, at a fourth or fifth injection, increased serous discharge may become noticeable. The time relations in the appearance of these different symptoms differs, however, very much; also the duration of the first period, which extends usually from the first to somewhere between the fifth and tenth injection. Then the second period begins, characterized by a decrease in secretion; generally the secretion may become less and less during this period, and the ulcer becomes not infrequently almost dry; the swelling and the redness which existed previous to the treatment also often begins to subside. Quite marked in many cases is the diminution of pain during this stage, sometimes, however, a little earlier, during the first period. The second period is a period of reaction against the first period of more or less intense inflammation. Immediately following the injections there may, however, during the second period still be present local inflammatory reactions, varying in intensity in different cases and at different times in the same case. This second period is also the time when the more definite healing processes set in in cases in which such reactions can be observed. This second period gradually grades quite slowly into the third period of immunity against the local effects of the injections. Just as in the case of the general reactions, the immunity is usually not a complete one in the case of the local reactions; even toward the end of treatment severe local reactions may follow an injection; but gradually the severity becomes less. In some cases these reactions may be absent altogether, especially after a late injection of colloidal copper. Just as in the case of the general reactions, casein immunizes

also against the local effects of colloidal copper, while on the other hand injections of colloidal copper do not immunize against the effects of casein.

These periods, however, cannot be demarcated so sharply in all cases. There was, for instance, a case in which it required seventeen or eighteen injections for the diminution in secretion to become apparent, and this change in secretion was apparently the only difference between the different periods in this case. In another case local reactions appeared as late as the thirty-fourth injection of colloidal copper (throbbing pain around the tumor). In another case the first period extended over the first ten injections, and was therefore rather long.

In these three cases in which there was either no marked demarcation between the different periods, or the first period was of a long duration, the healing effect was also extended over a longer period than in the other cases. In these three cases (Nos. 1436, 1502, 1405), immunization against the effect of colloidal copper evidently took place to a less extent than in other cases.

Just as in the case of the general reactions, we have also in the case of the local reactions to take into consideration the fact that the doses of colloidal copper as well as of casein were in a number of cases gradually much increased as the injections progressed and that therefore a partial immunity may have been masked through the strong effects of large doses. The local reactions which we described were, naturally, mainly observed in the case of superficially situated tumors. But they occur also, as far as we can judge, in internal cancers and in lymph-glands with metastatic growths and internal organs in which metastases have formed.

Such lymph-glands also swell and become painful after injections of colloidal copper or casein during the first period. In one case of a primary carcinoma of the rectum with metastases in the liver, the first injection of 25 c.c. of a solution of casein was followed by pain in the liver region, evidently due to hyperemia in the liver surrounding the tumor. If a lymph-gland with metastatic nodules is connected through a fistula with the surface, the increased formation of transudate in the lymph-glands after injections may become apparent. In the second period we may also observe in the glands a diminution in the swelling and secretion. In a case of carcinoma of the esophagus there was less pain in swallowing after the ninth injection of colloidal copper. We may assume that this was due to a decrease in the swelling of the tumor with the onset of the second period. Similar phenomena were observed in a cancer of the breast. The breast as well as the neighboring lymph-glands became painful after injections of colloidal copper. After injections of casein there was also pain present in the axilla and in the

neighboring enlarged glands. Combined with severe general reactions following injections of casein, the pain could be present on days following the day of injection; in this case the fever also extended over a number of days. In the same patient the breast was swollen for one day after another injection of casein had been given. Here, too, we have to assume that increased hyperemia and perhaps increased transudate was the cause of these changes.

In a number of cases of ulcerating cancers we observed that after a relatively small number of injections the discharge from the ulcer, which had previously been putrid, changed its character and became very much less putrid. A possible explanation for this phenomenon is the bactericidal action of the serous transudate which, as we stated, is increased during the first period or perhaps at a somewhat later day; the succeeding increased dryness of the ulcer may also perhaps bring about this result.

While the local reactions may be concerned in the healing process, they are certainly not the only factor determining retrogressive changes in the tumors. The character of the lesion and the general condition of the patient also play a part. Thus we notice that the local reactions may still be present at a time when the healing processes have ceased. There were some other cases in which healing processes took place without marked local reactions or in which healing processes took place at a time when the local reactions had ceased. The opposite also occurs: there may be present marked local reactions without any healing processes being noticeable. On the other hand, we have stated already that in cases in which healing processes are noticeable, they usually set in with the second period. In one case especially a certain connection between local reaction and decrease in the size of the tumor was noticeable. In this case (No. 1405) the thirty-fourth injection of colloidal copper was followed by throbbing pains in the tumor, and in the course of the following few injections the size of the tumor diminished noticeably.

We may therefore conclude that while the local reactions following the injections are in some way directly or indirectly concerned in healing processes taking place in the tumor, these local reactions are not the only factors concerned, but other factors may be of equal or even greater importance for the healing process.

If we now inquire into the mechanism of these local reactions, it appears most probable that the presence of the tumor with the constant development of new vessels produces a special, labile, sensitive condition of the vessels in the tumor as well as in the surrounding tissues. In consequence stimuli, as, for instances, the presence of certain foreign substances, though unable to alter to any noticeable extent the

blood-vessels of normal tissues, have, in contact with these labile vessels, a similar action as the localized injection of certain very irritating substances in the case of normal tissues. In the production of pain the central nervous system is concerned. The radiation of the pain to a symmetrical part of the body (other arm) suggests an irradiation of stimulation within the central nervous system.

It is not probable that such localized reactions are restricted to real tumors, but it is probable that other localized lesions react in a similar manner. This is indicated by one of our cases in which local reactions took place at a time when in all probability the tumor was no longer present, if, indeed, at any time a real tumor had existed in this case.

II. CHANGES IN TUMORS REPRESENTING HEALING PROCESSES

Among the local effects we have already mentioned, some changes induced by the injections which, inasmuch as they brought some relief to the patient, might in a wider sense be classed among the healing processes, as, for instance, decrease in pain, which was marked in a number of cases, decrease in secretion and in putrefaction, diminution in the swelling in the tissues surrounding the tumors or in the tumors themselves. In regard to the latter it is in certain cases difficult to distinguish between the decrease in size due to circulatory changes and a decrease in size due to the destruction of tumor cells, both processes occurring. It will be necessary to consider briefly the effect of the injections of colloidal copper and casein in a few selected cases.⁷

A. NON-KERATINIZING, CYLINDRICAL-CELL CARCINOMAS OF THE SKIN

CASE 8 (No. 3614).—In part reported previously. Man, white, aged 34. During first period of the treatment observations were made by Dr. M. F. Engman and incorporated in our previous reports.⁸ Multiple carcinoma of the skin on hand, face and neck. Numerous small cancerous ulcers, deeply infiltrating carcinomatous masses, destroying part of the nose, part of the skin in angle of eyes, some parts of lower lip. Lower lids of both eyes eroded. In tissues of left side of face were hard nodes of pea size. Lower lip greatly thickened, hard and everted. Skin rough and scaly. Three elevated plaques on the dorsal side of the hand. Disease started twelve years ago. Roentgen-ray treatment was tried without benefit. Thirty-six injections of colloidal copper; a large number of injections of casein extending over a period of more than four months. The injections of colloidal copper had no or only a very slight effect; our own interpretation of the action of colloidal copper is therefore less favorable than that of the first clinical observation of this case. There was perhaps a slight shrinking in the lesion of the nose; some crusts fell from the lesions, but similar changes had, as we found later, occasionally taken place spontaneously before the treatment was begun. The second injection of casein which had such marked general effects also led to marked local effects on the

7. For the sake of brevity, all other cases, comprising some of patients who were benefited, as well as the majority of those cases in which the results were slight or negative, are omitted.

8. Interstate Med. Jour., 1913, xx, No. 1.

tumor. Twenty-four hours after this injection many lesions appeared as if cauterized; after four days scabs fell from a number of lesions. The lesions of nose and upper lip healed almost entirely with the formation of scar tissue; some of the nodules of the lower lip became softer and disappeared. Some small lesions in the face disappeared; others remained unchanged. The following injections of casein had no marked effect. During the following six

Fig. 1.—Photograph taken before any improvement was noted. (Case 8.)

weeks some of the lesions became softer. At a later period, when immunity had been established, one nodule around the face began to grow again. In a nodule examined microscopically towards the end of the treatment many mitoses were visible. The histogenesis of this tumor has been described elsewhere.⁹

9. Loeb and Sweek: Jour. Med. Research, 1914, xxviii, 235.

The photograph (Fig. 1) shows the condition of the patient at the beginning of the injections of colloidal copper. It shows the large carcinomatous ulcers around the nose and the upper lip. The small lesions in the face, the swelling and ulcers of the lower lip are brought out only indistinctly.

The photograph (Fig. 2) was taken three and one-half months after the beginning of the injections of casein. It shows the healing of the carcinomatous ulcers around the nose and the upper lip. At that time the swelling of the lower lip had become definitely smaller and the ulcerated masses were also somewhat smaller, but had not disappeared. Later this patient was again treated with Roentgen rays without marked benefit.

Fig. 2.—This photograph is not recent. The patient is in better condition than the photograph shows. (Case 8.)

CASE 9 (No. 1502).—Man, white, aged 57. Disease began as a small black speck below the eye twenty-five years ago; the lesion grew very slowly. Several plaster treatments led to temporary improvement only. Gradually the eye became involved. Nine years ago Roentgen-ray treatment was given, producing an improvement lasting one year. Eye extirpated. The ulcer grew more rapidly within last five years. There is now a crater-like ulcer involving socket of eye as well as the cheek below. Seventy-three injections of colloidal copper were given within a period of ninety-seven days. Twelve hundred c.c. was the largest single dose given. After the fifth injection an island of new skin began to appear; it increased later to finger-nail size. After seventeen or eighteen

injections the discharge diminished and was less putrid. The ulcerated surface looked healthier. Improvement continued. After the forty-fifth injection new skin extended from the margin of the ulcer deeply into the ulcerated area. The ulcerated area showed a raw surface with numerous patches of what appeared as granulations; some well-marked blood-vessels. During the period between the fiftieth and sixtieth injections the ulcer was again covered with some pus. From the fiftieth injection progress was slow, but the newly formed skin extended somewhat, showing, however, a macerated appearance. After the sixty-first injection there was less discharge, blood-vessels and skin extended somewhat. At the time of the sixty-third injection one Roentgen-ray exposure was given; two days later the general appearance of the ulcer was improved; some more new healthy skin appeared, a few days after the first and second exposures to Roentgen rays. Powder was applied over the ulcer; this led to improvement, diminishing the macerating action of the secretion. During nine days there was no treatment. After sixty-six injections the ulcer was almost entirely covered with skin. Some discharge was still present, originating in the eye-stump, at the seventy-third injection. The ulcer, with the exception of a small area along the side of the nose and at the outside corner of

Fig. 3.—This photograph was taken before treatment of any kind was employed. (Case 9.)

the lower edges of the former ulcer, was covered with new skin. At the end of the treatment most of the ulcer had healed over. There remained still a small ulcerated area one-half as large as a dime at the lower margin of the former ulcer and another one near the eye-stump. It is of interest to note that the progress continued, although the general reactions after the injections were usually slight. In this case we have much longer-continued effect than usual. The two Roentgen-ray exposures may have contributed to the improvement. Of interest also is the healing over, notwithstanding slight local and relatively slight general reactions.

The photograph (Fig. 3) shows the condition of the ulcer before treatment. At no place was the ulcer covered with new skin. Figure 4 shows the condition toward the end of April, after about sixty-three injections and immediately after a second Roentgen-ray exposure. The ulcer looks much cleaner and a bridge of newly formed skin traverses the ulcer.

Figure 5 shows the condition of the patient at the end of the treatment. The ulcerated area is almost entirely covered by skin; only two small places are still uncovered. This condition was still present three months after cessation of treatment. Here also immunity took place. Some small places did not heal over.

Fig. 4.—Patient shown in Figure 3 after about sixty-three injections and immediately after a second Roentgen-ray exposure. (Case 9.)

Fig. 5.—Same patient as in Figures 3 and 4, showing the condition at the end of the treatment and also three months afterward. (Case 9.)

CASE 10 (No. 1436).—Woman, aged 69. In part previously reported. One year before the treatment was begun there was present on the bridge of the nose a small pearly growth with some ulceration in the center of the lesion. In the right ear involving the lower third and the auditory meatus, was an extensive destructive ulceration with considerable infiltration and swelling anterior to the mastoid process; the submaxillary lymph-glands were palpable. The lesion on the nose had at that time been present for one year; the lesion on the ear for three years. The patient was given Roentgen-ray treatment every other day until a reaction was produced on nose and ear. When the reaction had subsided, the nose was well and the lesion in the ear improved. She was soon given a second series of Roentgen-ray exposures without showing the same improvement as formerly. The tumor in the ear became larger and in the surrounding skin of the face and part of the scalp there developed eczematoid dermatitis. Staphylococcus vaccines and local antiseptic applications did not improve the dermatitis noticeably. The patient received in all seventy-eight Roentgen-ray treatments and when she entered the hospital in 1912 the tumor of the ear had grown double the size and the lesion on the nose had relapsed to its former condition. There was a discharging ulcerated patch beneath the ear and a tumor mass involving the seventh nerve, producing complete paralysis of the right side of the face. The patient received sixty-two injections of colloidal copper in seventy-eight days; usual dose 400 c.c., occasionally less; later nine injections of casein (2 to 8 c.c.). Corresponding with the onset of the second period healing set in. After the tenth injection of colloidal copper the ulcer appeared slightly shrunken, showing a thin dried scab. After the fourteenth injection the ulcerated area had several islands of new skin, also a line of new skin on the lower border extending upward over the ulcer. The skin around the ulcer appeared very much cleaner. After nineteenth injection the discharge had ceased, except from the auditory canal. The ulcer had healed from below upward, leaving a raw surface about as large as an adult middle finger nail. The skin around the ear was almost normal in appearance; only slight scales were noticeable, where before thick yellow crusted areas existed; clearing up of the eczematoid condition of the skin was simultaneous with healing. During the period from the nineteenth to the twenty-sixth injection the ulcer continued to shrink in size and a healthy crust formed over it. When the crust fell off, the ulcer beneath showed a healthy-looking skin; there existed no redness, edema or infiltrated margin around the ulcer. There was some discharge still from the meatus. After the twentieth injection the glands of the neck also were smaller. After the twenty-fifth injection dermatitis disappeared. Up to about the fortieth injection progress was still present, but slow. New formation of skin progressed, until at the end of the period only a small ulcer remained just below the auditory meatus, connecting with the ulcerated area in the external auditory meatus. During the rest of the colloidal copper injections an ulcer of the size of a split pea remained under the external meatus. After the use of bismuth paste, the skin gradually extended toward the meatus, but no complete healing took place. The principal progress was therefore during the first twenty injections; it depended mainly on the contraction of the skin; but in the second place also on a healing over of new skin. There was some slight but continuous progress for more than two and one-half months. Then there occurred again a breaking down over a small area under the external auditory meatus. On the back of the left hand there was a large scab which would form, come off, and leave a raw, ulcerated surface beneath. After fifteen days' treatment no difference between the two hands was noticeable. The hand remained healed. The lesion on the nose had not disappeared, but was smaller, only a small ridge being left. The skin over the area formerly occupied by the growth under the ear showed some redness and appeared to be thinner than normal skin and had a tendency to form small white scales, which were easily removed. In this case the general

reactions after injections of colloidal copper were slight and cannot be held responsible for healing processes in the tumor.

The casein injections had no effect. During that period the ulcerative process even extended a little beneath and behind the ear for a few weeks and remained from then on stationary. Casein produced much stronger general

Fig. 6.—Photograph taken before any perceptible change had occurred. The dark spots outside of the ulcerated area are small ulcerated nodules. The date card covers a large mass of glands. This mass is easily palpable and slightly raised above the skin surface, but not sufficiently to show in a photograph. (Case 10.)

reactions than colloidal copper. Microscopic sections through the tumor at the time when it was beginning to progress a little, showed some strands of non-keratinizing carcinoma with a number of mitoses.

In this case there is a distinct immunization against the effect of colloidal copper noticeable. The main result was obtained in the period between the tenth and twentieth injections. From then on to the sixty-eighth injection the progress was much slower and during the period of casein injections the tumor even extended slightly. The healing remained incomplete. Later Roentgen rays were used without leading to a complete healing.

The first photograph (Fig. 6) was taken before any perceptible change had occurred. The dark spots outside of the ulcerated area represent small ulcerated nodules. The paper showing the date when the picture was taken covers a mass of swollen glands. The second photograph (Fig. 7), which was taken after the injections had been discontinued, shows that the large ulcerated area

Fig. 7.—Photograph of patient shown in Figure 6, taken after the injections were discontinued. The large ulcerated area is now covered by healthy skin. The mass in the neck is gone. The small dark patch in front of the external auditory meatus is a patch that refused to heal, owing to the irritation of the constant discharge from the ear. Examination May 2, 1913, showed that this place had healed and that there was no further progress of the growth. (Case 10.)

seen in the first picture is now covered by healthy skin. At this time also glands in the neck were no longer swollen. The small dark spot in front of the external auditory meatus refused to heal as a result of the discharge from the ear constantly irritating it. This picture also shows the improved condition of the skin around the tumor; the scaly appearance seen in the first picture has disappeared.

Among four cases of so-called basal-cell carcinoma, two were markedly improved, while one showed only a very slight improvement. In the latter case we had to deal with an anemic person with a deep ulcer. In the fourth case colloidal copper was also without noticeable effect, while one injection of casein with marked general effects led to a partial healing. In the latter case we have to deal with an indirect effect of casein. We see, therefore, even in cases representing the same type of cancer, marked variations in the results of the injections.

B. CASES OF SQUAMOUS-CELL CARCINOMA

CASE 11 (No. 1455).—Man, white, aged 46. Three years prior to admission the patient had a sore on the lower lip; about two years later the sore began to spread. Treatment by paste made the condition worse. Now ulcerated area on right side of lower lip beginning at mucocutaneous border; hard everted edges; at lower half edges hang over to extent of 1 cm. Mass hard. Through mucous membrane hard nodules can be felt. Ulcer about $1\frac{1}{2}$ inches in diameter. An enlarged lymph-node under chin. Forty-six injections of colloidal copper (up to 500 c.c.) were given. Following the second injection of colloidal copper there was less pain. Following the seventh injection the edges of the ulcer softened; the ulcer was somewhat smaller. Following the tenth injection it was distinctly smaller; skin began to grow over the ulcer. These changes took place notwithstanding very slight general reactions. Up to the fourteenth injection the ulcer became still smaller. Following the seventeenth injection the nodule under the chin disappeared. After the twentieth injection the mass on the lip became still smaller, softer and could be folded. From then on only very slight changes occurred up to the thirty-first injection. The lip became movable; a little skin grew over the edge of the ulcer. During the casein injections there was no definite progress. Histological character of pieces taken out at an early and a late stage of the treatment was about the same. There was evidently in this case immunity produced after the first twenty injections of colloidal copper.

CASE 12 (No. 1476).—Man, aged 59. Carcinoma of cheek of sixteen years' duration. Cauliflower-like ulcerated carcinoma of left cheek of size of a 5-cent piece covered by yellowish-red scab, raised about 1 cm. above level of cheek. This growth was the center of an indurated area about two inches in diameter which was covered by reddened skin, extending down to but not involving the mucous membrane of the cheek. Could be distinctly felt on inside of mouth. Case declared inoperable on account of size of surrounding indurated area. Thirty-five injections of colloidal copper, eighteen injections of casein. From sixth to fourteenth injection the indurated mass around the tumor began to diminish in size; diminution continued up to the sixteenth injection. From then on there was a stationary condition. From the fourteenth to the seventeenth injection pain in the tumor disappeared. Central tumor not smaller, but easily movable. Casein without effect. Microscopically no change at beginning and end of treatment. Immunity after about fourteen injections; very slight general reactions in this case. After the series of injections the tumor could be apparently easily completely removed through operation.

CASE 13 (No. 1442).—Carcinoma of right cheek affecting lower jaw, extending to angle of jaw and into lower lip. In the lower part of swelling there is a protruding fungus-like ulcerated mass about three-fourths inch in diameter. Thirty-six injections of colloidal copper and twenty-seven injections of casein were given. Following the fourth injection of copper the external mass was somewhat reduced in size; following the tenth injection the tumor masses were smaller; soreness disappeared; patient opened mouth better. Fungus-like

outgrowth on outside of cheek had shriveled considerably and discharges less. After the seventeenth injection some shrinking in oral cavity; mass in mouth became movable; could open mouth much better; external prominence had shrunk. After end of copper treatment (Jan. 15, 1913) no copper found in section of tumor taken out. Four days after first injection of casein which produced marked general reactions, tumor noticeably smaller. Mass within mouth had diminished in size. The mass in the mouth which had been reddish before became grayish-white and appeared necrotic. Part of necrotic material was expectorated. Outer excrescence dried up. No change from further injections. Immunity began after ten injections of colloidal copper and was almost complete after twenty injections. There was also some immunity against general effects of colloidal copper. There was a necrotizing effect of first casein injection on the tumor.

CASE 14 (No. 1405).—Man, aged 74. Formerly reported; irregular ovoid mass apparently attached to periosteum over antrum. Continuous with this mass there is, in the buccal tissue, another swelling that appears on the mucous surface of the cheek as a leukoplakic area, raised about 2 mm. above the surrounding healthy mucosa. On gum and hard palate several small yellow nodules; sixty-two injections of colloidal copper (from 150 to 400 c.c.) From the seventh injection on, less pain in the face. After twelfth injection could open mouth and eat. From the twenty-fourth to the twenty-eighth injection, there were still less pain and further improvement in the general condition. No change in external mass of leukoplakia. During the period from the twenty-eighth to the thirty-sixth injections the external mass diminished steadily in size. At the time of the thirty-second injection the swelling was noticeably smaller. Following the thirty-fourth injection there was marked local reaction and subsequently swelling became markedly smaller and had disappeared after the thirty-sixth injection. Up to the forty-sixth injection the tissue continued to become softer and more movable, and the mass fixed on the periosteum could no longer be felt. Movements of the mouth were no longer restricted. Leukoplakic area and yellow spots persisted. No further changes took place. Up to the end of treatment microscopic examination of leukoplakic area showed much thickened epithelium with relatively small processes into the deeper tissue and some round-cell infiltration in the connective tissue below. There was a gain in weight during the period of injections. In this case there was no immunity against general reactions, and the main retrogressive change on tumor took place between the thirtieth and forty-sixth injections.

If we summarize briefly the effect of the injections of colloidal copper in cases of squamous-cell carcinoma (including some cases in which the microscopical examination could not be carried out), we find definite retrogressive changes in Cases 1404, 1442 and 1455, changes which could not be explained merely through alteration in blood and lymph circulation. In one case, T., in which the progress had been rapid before the treatment had been begun, at least a standstill followed the injections. In Cases 1499 and 1405 the diminution in the swelling was marked, but it is difficult to determine how much of it was due to alteration in the circulation through the tumor and surrounding tissues as the result of the injections. Such circulatory changes led also to a marked diminution in size in the Cases 1439 and 1298; in Case 1476 they were marked, but concerned the tissues surrounding the tumor proper; they rendered the removal of the tumor through operation possible. In the following cases there was only a

very slight or no retrogressive effect visible, or it was of such a kind that later experience made it doubtful whether the effect was due to the injections or to spontaneous changes: 1430, 1132, 1453, 1458, 1441, 1420, 1504, 1412, 1454. There were, however, some slight effects present in some of these cases; thus Patient 1412 could move the eye-lids, close the eye much better and could open his mouth much wider than before. Similar improvement was noted in Patient 1405. There was a decided diminution in pain in the following cases: 1455, 1405, 1458, 1404, 1439, 1412 and 1454. Putrid discharge was diminished in Cases 1458 and 1454. As to the effects of casein, we noticed in a manner similar to Cases 3614 and 1442, and to some extent in Case 1504, that an injection which has a very marked general effect on the patient may cause a part of the tumor to become necrotic, and later on to be cast off; the effect of such an injection does, however, merely affect a certain part and not the whole of the tumor. Otherwise it is doubtful whether injections of casein have any effect on the tumors, although they have more marked general and local inflammatory effects than injections of colloidal copper. There was perhaps a slight effect of casein present in Case 1420, in which the injections of casein preceded those of colloidal copper, and also in Case 1298. Of great interest is the fact that most of the healing changes, or changes leading to the relief of the patient, took place in the course of the first sixteen or twenty injections. Case 1405 was an exception in this respect. The principal changes took place, therefore, in the second period, or in the time directly following it.

In the following case the diagnosis of sarcoma could not be established with certainty:

CASE 15.—M., white girl, aged 16. Mother and grandmother of patient had been operated on for cancer. Swelling in right upper arm at junction of upper and middle third, about size of silver dollar, very sensitive to touch; pain especially on motion. Pain was noticed first about three months previously. Diagnosis of sarcoma was made by a well-known surgeon and immediate amputation of arm recommended. Roentgen-ray picture was taken before the injection was begun; she was kept under observation for twelve days; at the end of this period another Roentgen-ray picture showed that the growth had progressed. Circumference of arm at point of disease was 11 inches at the beginning and 11½ inches at the end of the period of twelve days. Six injections of colloidal copper (100 to 400 c.c.) and forty-six injections of casein in 117 days (from 15 to 25 c.c.) were given. After three injections of copper, five days after the beginning of the treatment, the circumference of the diseased arm had decreased ¼ inch. Directly following the first injections of casein there was an increase in the size of the diseased area, which was followed by a decrease. A Roentgen-ray picture five and one-half weeks after the beginning of the treatment (after about twelve injections of casein) showed a standstill in the disease; another Roentgen-ray picture was taken three or four weeks later which showed a new deposit of lime salts in the diseased part; this calcification progressed during the next few weeks; after the thirty-seventh injection about one-third of the area was infiltrated with lime salts. From then

on no or only very slight progress was made till the end of the injection. About three months after the last injection the diseased area was opened through operation. A cavity and necrotic bone were found; microscopically, connective tissue, partly rich in cells, was seen, and some necrotic bone invaded by connective tissue. In this case the diagnosis of sarcoma cannot be made with certainty.

In accordance with our previous observations, we found in a case of carcinoma of the breast that a single general reaction of great intensity following an injection of casein may lead to a partial destruction of tumor tissue. Injections of colloidal copper, in cases of cancer of the breast, led only to some diminution in the size of lymph-glands approximately coincident with the beginning of the second period. We treated three cases of carcinoma of the uterus; two of these were very advanced in very cachectic patients; one was less advanced in a relatively robust woman.

CASE 16 (No. 369).—Negro, woman, aged 30. Examinations by Dr. F. J. Taussig. Patient hysterectomized for carcinoma of uterus about four years preceding the injections. Recurrence. A mass the size of an orange, irregular in outline, palpable, was found in the right iliac region; a similar mass about one-half the size of an orange in the mid-pelvic region; about nineteen injections of colloidal copper (150 to 400 c.c.) were given.

After two days tumor on right side the same; in center a little smaller. After fifteen days right tumor smaller, tumor in center had continued to shrink and had become flatter. After twenty-one days pain had disappeared; there was very slight sensitiveness on deep pressure. No change in consistency. The right tumor continued to get smaller up to the end of treatment; the gland in the center was at that time hardly palpable. After discontinuation of treatment the disease began again to progress. There was no doubt in this case concerning the beneficial effect of the injections, which produced a considerable reduction in the size of the tumor and diminution in pain.

In a non-cachectic patient colloidal copper improved the condition of the patient markedly, causing a noticeable reduction in the size of the tumor. In this as well as in the one of the two cachectic patients, colloidal copper diminished pain markedly, while in the third cachectic patient neither tumor nor pain was influenced. We may furthermore conclude that the injections are capable of influencing, also, tumors other than those of the skin or external mucous membranes.

Some decrease in the size of the tumors was observed in a case of cancer of the thyroid. We leave it open in this case as to how much of this decrease was caused through circulatory changes.

7. CONCLUSIONS

I. SUMMARY OF EFFECTS OF COLLOIDAL COPPER AND CASEIN ON THE HEALING PROCESSES

1. Intravenous injections of colloidal copper have a definite effect in a certain number of tumors, while in the case of others they are without any noticeable effect. It is at present only to a limited extent possible to analyze the factors responsible for this variability in the

results. In a preliminary manner we may conclude that: A. The effect of the injections is not limited to a special kind of cancer. Definite results have been obtained in the smaller basal-cell as well as in squamous-cell carcinoma and in carcinoma of the uterus. The most marked results were, however, obtained with the least virulent, most chronic cases, namely, the smaller basal-cell carcinoma. B. Those patients in whom definite results were obtained were relatively vigorous persons. In cachectic patients and in those with internal metastases, no results were obtained, and in some cases it was observed that following an intermittent disease which weakened the patient very much, injections which had previously had some effect, became indifferent. C. While these factors seem to be of importance, other variable factors seems to play a part, and it is therefore impossible to predict in a given case whether or not a definite result will be obtained.

2. While in some tumors the measurable reduction in size, the shrinking of the ulcerated area, leaves no doubt about the definite effect of the injections on the tumor, there are a number of cases in which a noticeable shrinking of the tumor takes place, but in which the character of the tumors and the rapid effect of the injections suggest that the diminution in size is mainly due to an effect on the circulatory conditions in the tumor, as for instance, in Case 1439. In other cases, as, for instance, 1405 and 1513 (carcinoma of the thyroid), it is doubtful how much of the change observed is due to the circulatory changes and how much to an actual decrease in the quantity of tumor tissue. In one formerly rapidly progressing case the growth came to a standstill during the period of injections. In certain cases the injections do not influence to any noticeable extent the tumor itself, but they cause a marked diminution in the swelling of the surrounding tissues (especially in Case 1476). Through this sharp demarcation of the tumor proper a formerly inoperable tumor may become converted into an operable tumor. There was also an effect noticeable in the glands affected by metastases; a diminution in size was observed in a number of cases; again, changes in the circulatory condition may entirely or partially be the cause of this. In a number of cases a marked diminution in the pain, and, in some cases, in the quantity of the putrid discharge, followed the injections. In a considerable number of cases neither objective nor subjective improvement could be obtained.

3. In most cases the improvement began approximately with the onset of the second period (see general description of local reaction). In almost all cases the improvement after a temporary period of progress came to a standstill. The duration of the period of progress in healing varied considerably in different cases. We noticed a similar gradual decrease in the effects of the injections in the cases of the

general reactions and local reactions in the region surrounding the tumor. There was in some cases a parallelism noticeable in the curves indicating the gradual decrease in the reactions of a general character and those affecting the tumor directly. We may interpret this decrease in the effect of the injections on the tumors in two ways: A. Certain parts of the tumor or certain processes in the tumor are much more accessible to the actions of colloidal copper than others. After they have been influenced, other parts or other processes remain inaccessible to the effect of colloidal copper. B. An immunity is gradually obtained, not only against the general reactions, but also against those local reactions which induce healing processes. Inasmuch as we have proved the existence of such an immunity in the case of animal cancers, and have shown it to be of double origin, it becomes very probable that an analogous immunity is also produced in human cases. In addition, the first-named factor may play a certain part. Thus, it comes about that even in the apparently most favorable cases the healing remains incomplete and later even the progress of the carcinomatous growth may be observed. A similar immunity is produced against the general reactions following the injections of colloidal copper.

4. Microscopical examinations of pieces of tumor excised during different periods of the treatment do not indicate a direct destruction of the tumor. This is not conclusive evidence, however, against the occurrence of such a process, inasmuch as one of us has shown previously that also in definitely retrogressing animal tumors mitoses may still be found in tumor cells.¹⁰

5. While intravenous injections of colloidal copper have a definite effect, causing a partial retrogression in a certain number of cases, ordinary injections of casein preparations were even without effect or were followed by so slight effects that the distinct efficacy which can to a limited extent be ascribed to colloidal copper cannot be attributed to casein. In two cases, however, there were perhaps slight effects visible (1420 and 1298); these were cases in which the injections of casein had not been preceded by a larger number of injections of colloidal copper. We may interpret this lack of efficacy of casein in either of the following two ways: (A) Casein is actually without effect in human cancer, despite the fact that it is efficient, although to a less extent than colloidal copper, in animal tumors. Or (b) the lack of efficiency is only apparent, caused by the fact that in almost all our cases the injections of casein were preceded by injections of colloidal copper, and that through the preceding injections of colloidal copper an immunity had been produced against the action of casein as far as

10. Loeb: *Virchow's Arch. f. path. Anat.*, 1902, clxvii, 187; *ibid.*, 1903, clxxii, 363.

its direct effect on the tumors is concerned. Then it would be necessary to conclude that such an immunity against the direct effects of casein on the tumor could thus be produced, while, as we saw above, preceding injections of colloidal copper are not able to produce an immunity against the effects of casein as far as its general and certain inflammatory local reactions are concerned.

6. While a definite decision between these alternatives cannot be arrived at at present, we may definitely conclude that there is no thorough-going parallelism between the strength of local inflammatory reactions or the severity of the general reactions following the injections of a certain substance and its direct effect on the tumor.

7. In case injections of casein have an unusually marked general effect, causing high fever, extending over several days, combined with other severe symptoms, they may cause a partial destruction of the tumor within the next few days following the injection. This partial destruction may result in a localized process of healing. In no case was more than a partial effect accomplished by these means. This effect is in all probability not to be considered as a specific casein reaction, but it may be that any other substance causing very marked general reactions would have similar effects on the tumors.

8. As far as the general and local inflammatory reactions following the injections are concerned, our investigations have shown, in accordance with what we assumed from the beginning, that the local reactions around the tumor following the intravenous injections of various substances are in no way specific.

9. Some other investigators have made observations which support the conclusions that intravenous injections of colloidal copper, or of related substances, have a definite effect on a certain number of tumors, while others, the majority, are left uninfluenced. Thus Dr. M. J. Gelpi, in the Department of Gynecology at Tulane University, New Orleans, injected several patients with a solution of colloidal copper hydrate.¹¹ Among them he observed a case of carcinomatous ulcer of the cheek which healed entirely over as the result of the injections; an indurated area, however, remained unchanged.

Furthermore, there have also appeared reports by various observers in different countries, some on cases which show undoubtedly that injections of various colloidal metals have a definite, though, from a practical point of view, only partial, effect on a certain number of tumors. On the majority of tumors no or only a very slight effect could be determined.

11. A preparation of Mulford & Co., Philadelphia. We tested the same preparation in mouse tumors. See our communication in *Jour. Exper. Med.*, 1914, xx, No. 5. The case will be reported by Dr. Gelpi. In that case also a recurrence may have taken place later.

10. We have found some evidence supporting the conclusion that human and animal tumors are affected fundamentally in a similar manner by certain substances introduced into the general circulation. Colloidal copper has on cancer in animals a definite though by no means very strong effect. It has also an effect on a certain number of human cancers. We proved the existence of a process of immunization in the case of animal tumors after repeated injections of various substances and we analyzed its mechanism. While a proof of this immunity cannot be given in the case of human tumors with the same definiteness as in the case of animal tumors, its existence can at least be made very probable, a conclusion of theoretical as well as of practical importance.

II. SUMMARY OF EFFECTS OF INJECTIONS OF COLLOIDAL COPPER AND CASEIN NOT RELATING DIRECTLY TO HEALING PROCESSES

11. Colloidal copper, and probably also other colloidal metals, in contact with the walls of the veins cause pathological changes. Solutions of casein do so only exceptionally. The intensity of these changes depends on all those conditions which favor or inhibit an intimate contact between the colloidal particles and the endothelium of the blood vessels. The colloidal particles of metals produce, probably through injury of the endothelial cells, a greater permeability of the vessel-wall for the fluid constituents of the blood, and cause sometimes a dilatation of the vasa vasorum, leading to inflammation in the neighborhood of the vessels.

12. Immunity against the effects of colloidal copper produced through repeated injections of the solution is one of the factors determining the rise of temperature following the injection. The immunity produced against the effects of colloidal copper on the temperature is not specific; it can be produced through preliminary injections not only of colloidal copper, but also of casein.

13. Under similar conditions very small doses of casein cause a greater rise in temperature than colloidal copper, and the fever curve is steeper after casein. In individual cases the rapidity with which the fever disappears varies very much; it is probable that the duration of fever depends at least partly on the time during which unchanged or only slightly changed casein circulates in the blood, while in later periods, when the organism is in a position to split the casein more rapidly, the temperature returns more rapidly to the normal point.

14. Injections of casein are followed by an immunity against the general effects of casein; this immunity gradually increases with the progress of injections. It appears as early as after the first three or four injections; on the whole, three periods can be distinguished in its

development. Immunity may be established in strong as well as in weak persons, in whom there may be metastases present at the time the injections were given. Intervals of ten or nineteen days may elapse between two succeeding injections of casein without the appearance of definite symptoms of anaphylaxis. While preliminary injections of casein protect against the general effects of colloidal copper, preliminary injections of colloidal copper do not diminish markedly the effects following the injections of casein. There exists a certain parallelism in the curves of immunization following injections of casein and of colloidal copper.

15. Intravenous injections of colloidal copper or casein, if given through a considerable period of time, cause a relative increase in (especially small) lymphocytes and a corresponding decrease in polynuclear neutrophil leukocytes. This change extends over a long period of time and may still be present many months after injections have been suspended.

16. Intravenous injections of colloidal copper and casein cause in and around the tumors changes which might be characterized as a localized experimentally-produced inflammation called forth at a place distinct from the place of injection through substances introduced into the general circulation. Colloidal copper and casein produce essentially the same "inflammatory" reaction, only after casein the reactions are usually more severe.

17. We can in most cases distinguish three periods as far as the character and intensity of the local reaction is concerned. In the first period all the inflammatory signs are most pronounced. The second period is characterized by a marked decrease in inflammatory reactions. In cases in which the injections lead to an improvement in the conditions of the patients, the healing changes usually set in with the second period; the second period represents a reaction against the first period. The third period is the period of more or less marked immunity against the effects of the injections. Just as in the case of the general reactions, so also in the case of the local reactions, an immunity usually becomes established, which in this case likewise is usually not complete. In a similar manner as in the case of the general reactions, casein immunizes also against the local effects of colloidal copper, while, on the other hand, injections of colloidal copper do not immunize against the effects of casein.

While a certain connection between the local reactions and the healing processes seems to exist, the parallelism is not a complete one, probably owing to the interference of other variable factors.

It is possible — and we regard this as entirely tentative — that the reaction against the acute inflammatory changes of the first period, a

reaction which characterizes the second period and which leads to a diminution in the size of the tumor and its neighborhood mainly through circulatory changes, constitute the essential effect of the injections of colloidal copper, and that in some special cases this change is followed by further healing processes, either by a more marked shrinking of the tumor or by a healing over of the carcinomatous ulcer. Whether an actual destruction of tumor tissue takes place directly or indirectly as the result of the injections, can neither be positively asserted nor denied at present.

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