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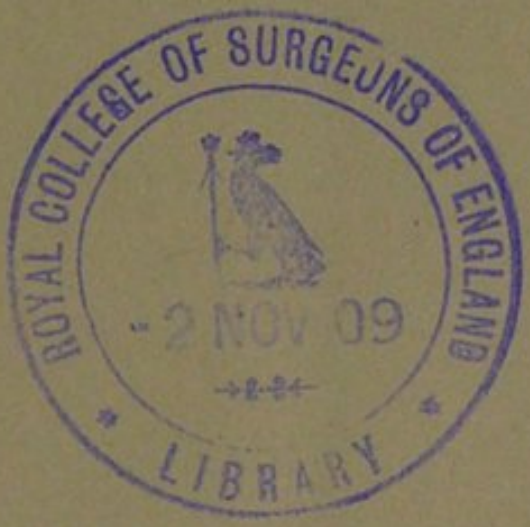

# THE ENZYME TREATMENT FOR CANCER —FINAL REPORT.*

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In a previous communication—"Trypsin in Cancer, a Preliminary Statement," published concurrently in the *British Medical Journal* and the *New York Medical Journal,* March 2, 1907—I expressed the determination of giving to the "enzyme treatment," as outlined by Dr. John Beard of Edinburgh, a thorough, scientific test, in a sufficiently large number of cases and over a long enough period of time, to warrant some claim to finality when conclusions were drawn. It was pointed out that many months must needs elapse before such a test could be reported in full. Now, after an interim of more than two years since the "preliminary statement" was made, and full three years since I began to employ

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The entire report, including four case reports and table of one hundred cases which appeared in the Record of Aug. 7 is published in bulletin form. This bulletin is on file in all medical libraries.

the enzyme method, it would seem that a final report may be offered which will meet the requirements of what may be called a "fair test."

No explanation need be offered to those who have read the leading medical journals, American and European, during the last four years and more for having given to this method of treating cancer the fair trial which its originator so earnestly desired.

Dr. Beard succeeded in arousing the interest of a goodly number of the members of the profession, both in Europe and America, as is shown by the fact that more than one hundred articles have been written upon the subject, and that five hundred physicians, out of more than three thousand to whom letters of inquiry were sent by me as Secretary to the Committee on Scientific Research of the New York Skin and Cancer Hospital, have employed the method. Whatever might be one's opinion concerning the theories upon which the so-called "trypsin treatment" was based, there seemed quite enough of possible value in the method to warrant its trial. Furthermore, through the overzealous influence of certain medical writers for the lay press and a few premature enthusiasts within the ranks of the profession itself, the method was heralded far and wide, and patients soon began to make the demand that it be tried in their case. Hoping that it might prove, if not the boon which it had been pronounced, at least a helpful adjuvant, and believing that it would do no material harm, we proceeded with the test, report of which is now offered.

It is but just to all concerned—to Dr. Beard, who proposed the method; to Mr. B. T. Fairchild, who so skillfully prepared and so generously supplied the materials; to the physicians and surgeons who cooperated with us; to the laboratory workers; to the

bedside attendants, and to the patients themselves—to say a word concerning the difficulties involved in giving to a non-surgical method for the treatment of cancer a thorough and final test.

The New York Skin and Cancer Hospital furnished ample clinical material from which to draw a large proportion of the cases in which the method was tried. To employ it only in advanced, irremovable, and inoperable cases was simple enough, but such cases do not give a sufficient basis for a complete trial. The surgeon, who must look upon the matter not as a "pure scientist," but as a clinician and a humanitarian, cannot bring himself voluntarily to subject a patient with cancer in an early stage, when it is amenable to complete removal by surgical intervention (certain local superficial growths in the judgment of some being excepted), to experimentation with *any* non-surgical method, no matter upon what scientific basis it may be exploited. Consequently such a method may be tried in early cases only where, despite the surgeon's earnest advice, operation is positively refused by the patient. As will be seen, a number of cases of this class are on our list.

An enormous amount of time and patience and much money were necessary in following out the details of the treatment. Inasmuch as it of necessity extended over weeks and in some instances months, it was not feasible in all cases to care for the patients in the hospital, the individuals themselves not infrequently objecting to being so long away from home. Under these circumstances, when the patient could not afford the expense, it was necessary for us to furnish medical attention and employ trained nurses to administer the treatment and carry out the régime in the home after the patient's discharge from the

hospital. To follow up the records in all cases from week to week and from month to month in such a manner as to render possible an accurate report of each, meant, in many instances, tracing the patient from tenement to tenement, sometimes from city to city. Innumerable obstacles were encountered at every turn. We endeavored, however, to meet these as they arose, to follow the régime outlined as closely as was feasible according to the exigencies of the individual case, and to keep as accurate data as possible in each instance. We believe we have been reasonably successful, despite the many difficulties, yet with all our care we were unable to follow some of the patients to the end, or to the present time.

In this connection I wish to extend sincere thanks for their hearty cooperation in the work to the following: Dr. Martha Wollstein, Pathologist to the New York Skin and Cancer Hospital; Dr. James Ewing, Professor of Pathology, Cornell University Medical Department; Dr. F. B. Mallory, Professor of Pathology, Harvard University Medical School; Dr. S. Elizabeth Finch, Assistant Pathologist to the New York Skin and Cancer Hospital; Dr. F. M. Jeffries, Pathologist to the New York Polyclinic Medical School and Hospital; Dr. F. D. Jessup, of the Department of Pathology, College of Physicians and Surgeons; Dr. E. E. Smith, Pathologist to Fordham Hospital, and others, for their valuable assistance in the laboratory phases of the work; Dr. J. Douglas Malcolm, of the staff of the New York Skin and Cancer Hospital, for his assistance in administering the treatments and following up the cases after their discharge from the hospital; Dr. Loy McAfee Inghram, Statistical Secretary to the Committee on Scientific Research of the New York Skin and Cancer Hospital, for accurate collation

of scientific data, and the various graduate nurses who have so carefully executed the details of the regimen in the homes of many of the patients. Especially do we wish to express our appreciation of the generosity of those who have been kind enough to contribute funds toward covering in part the necessary expense entailed in the successful conduct of the work.

**The Method.**—It is not necessary for the purpose of this report to review the interesting, if not generally accepted, embryological theory of the cause and development of cancer upon which Dr. Beard founded his method of treatment. The "irresponsible trophoblast" does not concern us here. Those not familiar with the theory can easily become so by reference to Dr. Beard's printed works.

Suffice it for our purpose to say, that at all times during the trial of the enzyme treatment I have been in close touch with Dr. Beard, and have followed the essentials of his method in all respects save one. When I first began to test the treatment Dr. Beard advocated its use in all cases after operation for the removal of cancer, whether primary or secondary, and in all inoperable cases. In this I readily concurred. When, however, at a later date, he modified his views, and opposed the removal of any "living cancer," declining to accept as a scientific test any case in which there had been previous operation, of course I demurred. This demand was met, however, as we have already seen, in cases where operative intervention was positively refused. We feel, therefore, that while the method has not been tried exclusively in such cases, we have been able to test it in a sufficient number to meet this requirement with justice to Dr. Beard's modified views.

In addition to the use of the enzymes, many details of management were urged by Beard. His various suggestions were incorporated by me in the directions for the "full regimen," and were employed in our test, with modifications to suit the needs of the individual case. In the reports and the table of cases which follow, unless otherwise specified, this regimen was executed in every instance, a copy of the directions being given to each one who administered the treatment.

DIRECTIONS.

1. *Physical Examination,* accurate and complete, made upon commencement of the treatment.

2. *Records* of each case, accurately and fully taken *daily,* with *weekly* records of the condition of the urine, blood, and, if possible, blood pressure, and weight. Both subjective and objective symptoms to be carefully noted.

3. *Diet,* wholesome and nourishing, with very little salt and no acids. Large quantities of water to be taken by the patient.

4. *Exercise* moderate.

5. *Hygienic surroundings* as good as possible, with abundant fresh air.

6. *Oral Treatment:* (1) *Holadin,* 1 capsule t.i.d., one hour before meals. (2) *"Pepule" oxgall compound,* 1 or 2 pills at night, according to requirements (to give tone to the bowels).

7. *Local Treatment: Lotio Pancreatis.*—To the quantity required for a single application, add an equal volume of freshly distilled water (unless ordered to be employed undiluted) and apply freely. Use twice daily, flushing the surface carefully with boiled water previous to renewal of solvent.

8. *Hypodermatic Treatment:* (1) *Injectio Tryp-*

*sini* (Special XX). Begin with ten minims daily, increasing five minims each day until some marked reaction takes place, or until two ampoules (20 minims each) are being taken each day.

(2) *Injectio Amylopsini.* When the trypsin injections have been increased to 40 minims daily injections of amylopsin are then begun on alternate days with trypsin, never on the same day. Commence with ten minims, increasing five minims each day until the maximum dose is reached, viz., 40 minims of trypsin one day and 40 minims of amylopsin the next.

Before making the injections apply ethyl chlorid to the surface to be injected (preferably over the buttocks), or inject 1/10 grain eucaine, then inject the trypsin or amylopsin into the deeper subcutaneous tissues, not into the muscles.

*Note* 1. The greatest care, cleanliness, and nicety in every detail must obtain.

*Note* 2. The doses must be regulated with careful regard to the reactions observed.

*Note* 3. The contents of the ampoule must be used *only when freshly opened.*

*Note* 4. The ferments are destroyed by antiseptics; care must be taken therefore not to render them inert by contact with such substances.

*Note* 5. If there is any local irritation from the injection, despite the greatest care, dilute with equal parts of distilled sterilized water before injecting, or with equal parts of sterilized normal salt solution.

*Note* 6. The general condition of the patient must be given careful attention. As little narcotic medication should be given as possible, tonics and predigested foods, if indicated. Elimination by bowels, kidneys and skin is of the utmost importance.

*Note* 7. The treatment, after well started, is said to have a definite control over pain. Over-drugging should be avoided in order that this claim may be carefully studied in relation to the cases.

*Note* 8. Injections of amylopsin should not be given while the patient's stomach is empty, as the tendency to nausea is increased under such circumstances.

*Note* 9. If irritation results from the introduction of the entire injection in one locality, this may be overcome in the following manner: Introduce the needle tip into the tissues, inject a portion of the material, withdraw slightly, introduce in another direction and inject another portion, and so on until the entire amount is inserted into the subcutaneous tissues in "puddles" at some distance from each other, but with one common point of puncture. By taking this precaution the tissues will not be overdistended, and the tendency to irritation will be lessened. The needle should be inserted obliquely so that the material will not escape in part through the puncture point.

Abscess formation, so-called, was noted in some cases, and has been reported by a number who have employed the method. Real abscesses are due to (1) faulty technique; (2) localization of infection in cases where there is a general condition of sepsis from absorption of broken-down material; (3) from a complicating infection such as tonsilitis or la grippe. The so-called "trypsin abscess," on the other hand, has been shown by examination of the material to be not a true abscess, but unabsorbed trypsin solution with some broken-down tissue cells. After prolonged treatment the tissues in some cases fail to absorb the material which, in time, breaks down, is discharged, and a sinus is left for a while.

**The Materials.**—We are indebted to Mr. B. T. Fairchild for the materials employed. They consist of the following: (1) Holadin capsule, a pancreas gland extract containing all the pancreas enzymes—trypsin, amylopsin and lipase—and the milk-curdling ferment. This is given to aid digestion. (2) "Pepule" oxgall compound, which contains inspissated oxgall, extractum pancreatis, and extract of nux vomica. This gives tone to the bowel and aids in elimination. (3) Lotio pancreatis, a glycerin extract prepared directly from the fresh gland and carrying in solution the entire soluble gland constituents. This solvent of broken-down tissue is applied topically to the ulcerating surfaces. (4) Injectio trypsini, a glycerin extract of trypsin, which, according to Beard, was supposed to "kill" the cancer cells. (5) Injectio amylopsini, a glycerin extract of amylopsin, which was thought to "digest" the dead cancer cells.

The first pancreas injections were made of a proteolytic power equal to 2 per cent. of trypsin, and adopted in consequence of a strength or "percentage" of trypsin, at first extemporaneously prepared and used by Beard and others. The medium, 60 per cent. glycerin, had already been found to meet the requirements, containing the enzymes of the fresh pancreas extract in an active and sterile condition. This, however, necessitated preliminary dilution in making the injection ready for use. Gradually clinical experience warranted an increase in tryptic power, until finally this desideratum could be achieved only by a more aqueous medium, and consequent reduction to 20 per cent. glycerin. This lower content of glycerin afforded the advantage of increase of trypsin content and increase of dosage, as found in the ampoule.

The various injections of trypsin furnished for our use were identified for convenience of record as follows: "Regular," 60 per cent. glycerin, equal to 2 per cent. trypsin (dry); "Fortified," 60 per cent. glycerin, double the strength of the "regular;" "Special," 20 per cent. glycerin, double the strength of the "regular;" "Special XX," 20 per cent. glycerin, four times the strength of the "regular" (this was used in most of our cases); "Special Quadruple X," 20 per cent. glycerin, six times the strength of the "regular" (prepared especially for this test, and said at the time to be the strongest it was possible to make).

Injections of amylopsin of corresponding strengths were furnished us. The 20 per cent. glycerin amylopsin injection presents parallel advantages with the 20 per cent. trypsin injection, in increased potency, and in available volume of dosage without dilution. Thus, twenty minims of the 20 per cent. glycerin "Special" carries an enzyme potency corresponding to a sixty minim injection composed of twenty minims of 60 per cent. glycerin solution from an ampoule, with forty minims of diluent—sterilized water.

Having noted the strengths of the injections, it will be seen from the cases detailed later, how much stronger were the injections used in many of our tests than were those employed in the cases reported by a number of writers during the earlier months of the history of this method. The idea entertained by many at first, to the effect that only moderate doses of weak solutions of trypsin could be tolerated, was proved entirely erroneous in our experience. In many cases we were able to give daily two or three ampoules (twenty minims each) and in several instances 100 minims for days at the

time of the "Quadruple X" solution wih no untoward effects. From this it will be seen how absurd were some of the earlier claims of "cures," as well as of the strange symptoms and "terrific" results from the small doses employed.

A careful study of the blood and urine in a certain number of cases was made, under my direction and with valuable suggestions from Dr. Martha Wollstein. For the painstaking execution of this work, and the careful recording of the findings, credit is due to Dr. S. Elizabeth Finch.

**Blood Examinations.**—Blood examinations were made regularly over a period of ten months in a number of hospital and dispensary cases to observe what effect, if any, was produced by the enzyme treatment on any anemia present, or on the white cells of the blood. Leucocyte and differential blood counts were made once a week in the different cases, and hemoglobin tests and red blood cell counts were made as was deemed necessary. Upon placing a case on the treatment, in so far as possible, two, preferably three, blood counts were made on two or three successive days preceding the first injection; one count within twelve hours of the first injection, and then one every twenty-four or forty-eight hours for the first few days.

Blood examinations were made in thirty-seven cases, but in only nineteen did the observations extend over a period of more than four weeks, the treatment being discontinued for one cause or another, or the patient passing out from under observation.

Of the thirty-seven cases in which blood examinations were made, nine were epitheliomata and the rest carcinomata. There were no cases of sarcoma. In four cases of the thirty-seven no operation had

been performed, and the cases were still in the operable stage. In one of the four, however, complications contraindicated operation. Of the remaining thirty-three, six had not been operated upon, but were inoperable when the enzyme treatment was begun. The other cases (twenty-seven) were inoperable ones, in many of which exploratory or palliative operations had been performed. Ten cases (Nos. 33, 79, 86, 87, 89, 90, 91, 93, 95 and 98) were followed throughout the entire course of their treatment by the enzyme method.

In ten cases of the thirty-seven there was an anemia of the chlorotic type. In eight of these it developed only in the last stages of the disease. The other cases showed a mild varying grade of secondary anemia. Nucleated reds, of the type of normoblasts, were rather rare. The hemoglobin in the more severe cases varied between 45 and 75 per cent.; the number of reds from 2,168,000 to 5,580,000 per cubic millimeter. In no test was the hemoglobin ever higher than 85 per cent. (Fleischl hemoglobinometer).

In five cases there was an improvement in the hemoglobin during the first few weeks of enzyme treatment. In Case No. 32 there was an increase from 80 to 85 per cent., and a gain of 100,000 red blood corpuscles. The hemoglobin subsequently dropped to 70 per cent., the red cells remaining about the same. In Case No. 50 there was likewise an improvement of about 5 per cent. hemoglobin during the first two months of treatment. In Case No. 44 there was a gain of 12 per cent. hemoglobin and of nearly 700,000 red cells per cubic centimeter during four weeks of treatment. In this case the treatment was begun very soon after an operation and the gain can therefore be ascribed in but small

part, if at all, to the treatment. In Case No. 79 there was an improvement of about 4 per cent., which was subsequently lost. This gain was also post-operative. In Case No. 98 there was an increase of about 5 per cent., hemoglobin and an increase of 200,000 reds per cubic centimeter during the first four weeks the patient was in the hospital.

Leucocyte and differential counts were made in four enzyme cases and one control case (Nos. 79, 91, 92, 95 and 98) three times, at the same hour on three different days, before beginning the injections. In ten enzyme cases (Nos. 22, 33, 35, 36, 44, 49, 80, 86, 87, 89, 90 and 93) and two control cases (Nos. 35 and 90) leucocyte and differential counts were made once before the beginning of the treatment. In the remaining ten cases the blood examinations were begun after the patients had had the treatment for from one to thirty weeks. In a few cases which were carefully observed during the first week or two weeks of injections there was a gradual and moderate increase in the total number of leucocytes; however, in only two cases could there be said to be no other causative factor than the trypsin injections. In five cases of cancer of the breast there was no total leucocyte count over 12,500 per cubic millimeter which could not be ascribed to causes other than the cancer. In five cases of epithelioma there was no total leucocyte count over 9,500 per cubic millimeter not accountable for by necrosis, ulceration, or other complication. The counts on the cases in which there was marked ulceration and sloughing varied between 23,500 and 34,000 per cubic millimeter.

Blood smears were made in the mornings between one and one-and-a-half hours before the noon meal and at a corresponding hour in the individual cases.

Cases from the Dispensary came at corresponding hours between two and three P. M. The Wright stain was used as a rule, in some instances Ehrlich's triple stain. In making the differential counts 500 cells were counted, in some instances 1,000 cells, and in three instances only 300 or 400 cells. Over 300 differential counts were made.

The following classification was followed: polymorphonuclear neutrophiles, large mononuclears and transitionals, small mononuclears (size under polymorphonuclear), eosinophiles, mast cells, and myelocytes. Under the head of small mononuclears were included the non-granular mononuclear cell with central nucleus and small amount of protoplasm, and the mononuclear cells with small eccentric nucleus and non-granular protoplasm, present in larger amount than in the above. The size of these cells so counted was under that of the polymorphonuclear cells. For purposes of charting the per cents. of large mononuclears and transitionals were averaged together.

*Summary of Blood Examinations.*—A relative lymphocytosis was found at some time in the course of thirteen cases out of twenty here described. In two other cases observed over a period of three months, in which counts were not quite so frequently made and not here given, there was also a relative lymphocytosis found, making the number of cases fifteen out of twenty-two. The relative lymphocytosis was present sometimes before the beginning of the trypsin treatment, while injections were being given, and after treatment was discontinued. It was found at times in the control cases. When the course of the disease was apparently held in check the lymphocytes were relatively normal, below, or very slightly increased. In those cases in

which the disease was steadily progressing the small mononuclears reached the highest relative per cent., dependent in a measure, however, on the presence or absence of complications. In the presence of any complication causing high increase in the polymorphonuclear neutrophiles the small mononuclears were, as a rule, relatively low. Out of the fifteen cases above mentioned (four epitheliomata and eleven carcinomata), nine cancers were in such locality that extension by the lymphatics and glands would naturally follow. Four were pelvic and abdominal cases of cancer, in which any progressive glandular involvement was not demonstrable. One was a case of epithelioma of the lower jaw, in which the relative per cent. was quite high, but glandular involvement was not certain. In the other seven cases of the twenty-two, in all except one there was a complication present, causing a relative and absolute increase in the polymorphonuclear cells. This one case was observed only over a period of four weeks following operation.

It is desired to emphasize the presence of a relative lymphocytosis (increase of small mononuclears) found present in the course of the above cases (irrespective of treatment) in association with progressive growth of the cancer or metastatic formation, and, frequently, found present before increased growth or enlarged or new metastases were clinically demonstrable. With the exception of four cases out of the twenty that were observed over a period of from 6 weeks to 7 months, the eosinophile cells showed a steady increase in numbers while the patients were upon the trypsin injections. Upon discontinuing the injections the eosinophile cells dropped in numbers, reaching the normal average, or much below it, in about two weeks' time. This

fall in numbers per cubic millimeter occurred in every instance, although the internal treatment was continued regularly. If, because of refusal on the part of the patient or because of the general condition of the patient, two or three treatments were skipped, it was apparent in the temporary decrease in the total number of eosinophiles. In no case, however, was the relative per cent. greater than twelve, although the trypsin injections were in many of the cases pushed to the limit for the individual in question. There was no eosinophilia in any of the control cases except where there was involvement of bone.

The exact etiology of this eosinophilia is speculative. One cause which is suggested is the absorption or attempted absorption of the trypsin from the subcutaneous tissues. The eosinophilia does not entirely disappear when the patient is put on amylopsin injections after discontinuing the trypsin. This is so judged as the count falls still lower after discontinuing all injections. There were no nodules as the result of amylopsin injections. Incidentally it may be remarked that injections of amylopsin into trypsin nodules did not in any degree hasten their absorption. In cases on the internal treatment alone there was no eosinophilia observed, although it is claimed (von Leyden and Bergell) that trypsin passes into the general circulation from internal administration and may be absorbed in large amounts. In four of the cases in which there was rectal or other intestinal involvement eosinophiles were present before treatment in from three to five per cent., representing 300 to 700 per cubic millimeter. In three cases with bone involvement (not on trypsin) eosinophiles were present in from four to six per cent., representing 460 to 1,080 eosinophiles per cubic millimeter.

**Urine.**—In an attempt to ascertain if there was any irritating action exerted by the trypsin on the kidneys in the cases in which it was given by mouth, hypodermatically, or by other methods, ordinary urine tests were made in connection with twenty-three cases treated with trypsin. In eight cases uranalyses were made before treatment was instituted, then every day for the first week or ten days of treatment, and thereafter as was deemed advisable. In five out of this eight neither casts nor albumin were present at any time in the urine. In two out of the eight cases there was an occasional trace of albumin, hyaline and sometimes few granular casts in the urine before the injections were begun. This condition varied while the patients were on the treatment. In one instance there was a slight exacerbation in the kidney lesion following constant and rather large doses of the trypsin. In the remaining case out of the eight, the treatment was given for a week and then discontinued for a second operation, the removal of a recurrent nodule. Following this operation the patient had a slight cold, and when the uranalyses were resumed in connection with the trypsin injections, there was a small amount of albumin, finely granular and few hyaline casts present in the urine. The patient left the hospital soon after this, and while the treatment was continued for some time no uranalyses were made outside of the hospital. In this instance casts and albumin were not present before treatment or before the second operation.

In the urine of a few cases out of the other fifteen, of the twenty-three, granular, hyaline, and few pus casts, and occasionally albumin, were observed in the very last stages of the disease. With one exception they were not present at other times. In this

case, an old man over ninety, with epithelioma of the ear, there were constantly present the evidences of nephritis. The treatment had been given in large doses from the beginning, and the patient had had an acute exacerbation of the nephritis. Upon resuming the trypsin injections a second time, small increasing doses were used; it was this time taken for eight weeks, when symptoms of a beginning exacerbation of the nephritis became evident.

It was desired to study the execretion of the chlorides, phosphates, and sulhpates in connection with the trypsin treatment, but owing to the difficulty of securing a sufficient number of uncomplicated cancer cases from whom 24-hour specimens of urine could be regularly obtained this was not done.

The following method was used in testing the urine for an enzyme with properties of digestion similar to trypsin (see Hedin; *Jour. of Phys.*, Vol. XXX, 1903, pp. 155-195); also Cathcart; Products of Urotryptic Digestion, Salkowski's Festschrift, 1904). Urine with a specific gravity of 1011 and under was used undiluted, while urine with a specific gravity over 1011 was diluted one-third or one-half with distilled water for the following work. To each 1000 c.c. of the urine or urine mixture was added 5 c.c. of a 3½ per cent. solution of casein in 0.25 per cent. sodium carbonate. To less amounts 750 or 500 c.c. was added, 3 or 2½ c.c. of the 3½ per cent. solution of casein. The casein after thorough mixing with the urine was precipitated by 20 per cent. acetic acid. After complete precipitation the supernatant fluid was siphoned off and the precipitate transferred to a filter and washed free of acid with distilled water. After thorough washing the casein-enzyme combination was transferred in each case to

a six ounce sterile glass-stoppered bottle, which was then filled with 0.25 per cent. or 0.5 per cent. solution of sodium carbonate made with distilled water. To each bottle were added a few pieces of fibrin that had been boiled for fifteen minutes. Toluol and chloroform were then added to each bottle to prevent putrefaction. The various bottles labeled with date and name of patient were kept in the thermostat for from one to seven months, at a temperature ranging between 35 deg. and 37 deg. C.

Four cancer cases on the trypsin treatment and a control case (epileptic) were selected as suitable, and three times a week twenty-four-hour specimens of urine were heated and the casein separated out as above described. The casein combination in each case was transferred after thorough washing to a sterile six ounce bottle, filled with 0.25 per cent. sodium carbonate, and a small amount of *unboiled* fibrin added. Toluol and chloroform were added and the bottles placed in the thermostat as soon as they were finished. These digests were made over a period of three weeks. Upon examination daily there was evident a gradual dissolving of the fibrin, and at the end of six weeks the amino-acids were found present in each case. These findings led to the making of some control digests.

Two sterile six-ounce bottles were filled with 0.25 per cent. sodium carbonate made with distilled water, and to each one was added 2½ cubic centimeters of a 3½ per cent. solution of casein. Two other sterile bottles were filled with a 0.25 per cent. sodium carbonate, and 2½ cubic centimeters of a 3½ per cent. solution of casein, and a few pieces of unboiled fibrin were added to each bottle. To another series of two bottles which were filled with 0.25 per cent. sodium carbonate were added 2½

cubic centimeters of 3½ per cent. casein solution, and a few flakes of fibrin that had been boiled for fifteen minutes. To each of the above bottles were added toluol and chloroform and they were placed in the thermostat. Observed over a period of six weeks numbers I and II of the first series remained perfectly clear, a few grains of casein being demonstrable at the bottom of the bottles. Numbers I and II of the second series showed solution of the fibrin. Number I of the third series showed slight solution of the fibrin (boiled); number II of the third series showed no change in the fibrin. Upon examination for digest products (about six weeks' time) the casein was found unaltered in bottles I and II of the first series. In the second series to which unboiled fibrin had been added digestion products were demonstrable in both bottles. In number I of the third series there was some digestion; this bottle had been frequently opened and contained *very small* amounts of the preservatives. That the bottle became contaminated was evidenced later by its odor. Bottle number II of the third series showed no digestion.

Two more digests according to series III were made about one month later than the above. In this series number IV there was no digestion. During this month and the following there were many digests made from specimens of urine from different trypsin cases and control cases, to which the boiled fibrin was added; but not until March, 1908, was there a definite series of cases followed every day for a couple of weeks.

In March two cases on the regular trypsin treatment were selected, one a case of abdominal carcinoma, the other a case of carcinoma of the base of the tongue, epiglottis and glands of the neck. Two control cases were selected, one a patient not having

cancer, the other a cancer case, but not on the trypsin treatment. Twenty-four-hour specimens of urine (when possible) or single specimens were obtained from these four patients twelve out of seventeen consecutive days. The method above described was used in separating out the supposed casein-enzyme and preparing it in each instance for the thermostat. Boiled fibrin was used in the thirty-four digests made. These digests were all kept in the brood oven four months; twelve of them were afterward kept at room temperature for another three months. In eight instances out of the thirty-four there was no evidence of any digestion of the fibrin. In three more cases there was some dissolving of the fibrin, but the presence of any of the group of amino-acids could not be demonstrated. Thus there were eleven negative digests in the thirty-four. In one control case (not cancer) the results were negative five times out of seven, but positive in the other two cases. In the other control case two digests were negative. In the trypsin cases results were negative in one instance twice and in the other three times. In seven of these eleven negative digests the urines when treated were slightly alkaline from beginning ammoniacal decomposition. These urines were probably neutral or slightly alkaline when voided. In the four other negative instances all digests made on the two days these were made gave negative results. It is possible that the casein was not sufficiently well mixed with the urines to separate any enzyme present.

In the other twenty-three digests the amino-acid group was found present in each one.

The above experiments showed the presence in the urine in cases on the trypsin treatment, in non-cancerous patients, and in patients with cancer who

had not been treated by trypsin, of an enzyme possessing properties of digestion similar to trypsin. This body was not found in urines in which there was beginning ammoniacal decomposition. No attempt was made to ascertain the appearance or disappearance of the body in the urine during the various stages of a cancer case, which might be of interest in connection with the known anti-tryptic action of the serum in all cases of severe anemia, and said by Brieger and Trebing (*Berliner klin. Woch.*, July 20, 1908) to be present early in all cancer cases, and to be influenced by the administration of pancreatin as shown by a remarkable fall in this anti-tryptic action of the serum.

*Effect of Trypsin upon the Tissues.*—In submitting sections to pathologists for examination, in all cases where the tissues were removed after the institution of the enzyme treatment, it was requested that especial attention be directed to the determination of any structural changes that might in any way be attributable to the action of trypsin. Whenever it was possible to do so specimens were taken from time to time, care being taken in every instance not to encroach upon nature's barriers. Comparative studies were thus made of the pathological tissues before beginning the enzyme treatment, at various times during its course, and in some instances after the death of the patient.

Dr. F. B. Mallory, Professor of Pathology, Harvard Medical School, who made a number of examinations, found nothing that he could in any wise attribute to the action of the trypsin.

Dr. Martha Wollstein, Pathologist to the New York Skin and Cancer Hospital, who made the largest number of examinations during the course of

the test, found no tissue changes which could be ascribed to the action of the trypsin.

Dr. James Ewing, Professor of Pathology, Cornell University Medical Department, after careful study of the specimens submitted to him, made the following statement: "In several sections the central cells in many tumor masses were loosened, degenerating or necrotic, while only the outer layers of cells adherent to an infiltrated lymph space seemed to retain their vitality. In some cases of cancerous infiltration of the uterine muscle originally larger tumor cell masses appeared to have been reduced by this process to thin strands of degenerating epithelial cells, and in some rather wide areas the tumor infiltration took the form of isolated cells scattered at wide intervals. In some cases a peculiar edema and vacuolar degeneration was prominent, but this condition differed only in degree from that sometimes seen in untreated cases.

"Occasionally there was encountered a peculiar edema and granular degeneration and fragmentation of fibrous, connective, and smooth muscle tissues which I have not seen in untreated cases. In all the cases considerable portions of the growth appeared little or not at all affected by the above mentioned degenerative processes, a fact which may account for the steady clinical progress of the disease. In one or two cases there apeared to be no change whatever referable to the treatment."

**Summary.**—From careful clinical and laboratory observations, extending over a period of three years, the following deductions may be drawn:

(1) That the internal medication with Holadin and oxgall aids digestion and increases elimination.

(2) That lotio pancreatis applied locally clears the ulcerating surface by removing organisms, thus

aiding in diminishing the absorption of their products.

(3) That aiding digestion, increasing elimination (by skin, kidneys, and bowels), and decreasing local absorption are the most important features of the treatment.

(4) That the regime by increasing resistance may in some cases decrease the rapidity of the malignant process.

(5) That control cases given injections of glycerin and water or sterile water alone, plus the regime, did as well as those on the full enzyme treatment.

(6) That injectio trypsini, in some cases, seems to cause more rapid disintegration of (to "liquify," according to Beard) cancerous tissue.

(7) That while it may accelerate the breaking down in the center of the tumor mass, the periphery is found to be actively growing, as was true of Case VII (Case 1 of Dr. Morton's published series). When injected into the tumor itself this disintegration is more marked.

(8) That because of the tendency of injectio trypsini to disintegrate the tissues, it may be a direct menace to life (*a*) by eroding large blood vessels (when the disease is contiguous to these structures, as when deep in the neck or in the pelvis), thus causing death from hemorrhage; (*b*) when given in large doses, over considerable periods of time, by overwhelming the system with toxic products (tumor toxins), thus, in some cases, hastening death.

(9) That the injections are often painful, and patients many times refuse to take them.

(10) That the so-called "trypsin abscess" proved,

upon examination of the material, to be unabsorbed injectio trypsini plus broken-down tissue.

(11) That when real abscesses formed they were due to faulty technique, to localization of a general sepsis resulting from the absorption of toxic products, to an accompanying sepsis of whatever origin, or to a complicating acute infection.

(12) That injectio amylopsini seems to diminish cachexia in some cases, in accordance with the claims of Beard and others.

(13) That in some cases there was no reason to believe that injectio amylopsini exerted the action claimed for it.

(14) That when amylopsin was injected directly into the indurated area left after injecting trypsin, absorption of the trypsin solution was not hastened.

(15) That 100 minims daily of the "Quadruple X" solution, the strongest made, were given in some cases with no untoward effects.

(16) That improvement in hemoglobin (5 to 12 per cent.) during the first few weeks or trypsin treatment occurs in about one-sixth of the cases examined. In only one-third of these was the increase ascribable to the trypsin alone.

(17) That a gradual and moderate increase in the number of polymorphonuclear neutrophile cells was noted during the first two weeks of the trypsin treatment in a few of the cases.

(18) That with the exception of two cases such leucocytosis as was noted was attributable to the occurrence of complications during the first two weeks of trypsin treatment.

(19) That in fifteen out of the twenty-two cases above mentioned a steady increase (6 to 12 per cent.) in the number of eosinophile cells was noted while patients were on the trypsin injections. There

was no eosinophilia in the control cases, nor in the cases treated by trypsin given by the mouth.

(20) That eosinophilia occurred regularly in cases of carcinoma involving the bones or the intestines, even without the exhibition of trypsin.

(21) That the claims for eosinophilia as a test have not been substantiated in our experience.

(22) That albumin and casts were found in the urine before treatment was begun in two cases. In neither of these was the amount of albumin or the number of casts increased at any time throughout the continuation of the trypsin injections.

(23) That in severe cases in the very last stages of the disease hyaline, granular, few pus casts, and occasionally albumin, made their appearance.

(24) That in two other cases in which it was impossible to obtain specimens of urine before beginning the treatment, albumin and casts were present when the cases came under examination; and as the trypsin doses were increased the amount of albumin and the number of casts were increased.

(25) That dextrose was at no time found in any of the urine specimens examined, not even when untoward manifestations of trypsin were present and large doses of amylopsin were being given.

(26) That the series of experiments which were conducted for the purpose of ascertaining the presence or absence of an enzyme in the urine with properties of digestion similar to trypsin, showed the presence of such an enzyme body (irregularly present) in (*a*) trypsin treated cancer cases; (*b*) non-cancerous untreated cases; (*c*) cancer cases which had not received the trypsin treatment.

(27) That the exact constancy of this enzyme body in the urine with reference to the treatment was not ascertained. No enzyme body was found in

urines in which there was ammoniacal decomposition.

(28) That the enzyme treatment as administered in the cases herewith reported, and according to the suggestions of Dr. Beard, plus important details of regime, does not check the cancerous process.

(29) That it does not prevent metastasis.

(30) That it *does not cure cancer.*