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THE PHYSIOLOGICAL ACTION AND THERAPEUTIC USES OF YEAST NUCLEINIC ACID, WITH SPECIAL REFERENCE TO ITS EMPLOYMENT IN TUBERCULOSIS.[1]

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Nucleins and Nucleinic Acids.—I have elsewhere spoken of nucleins as follows: "Physiologically, nucleins may be said to form the chief chemical constituents of the living parts of cells. Speaking broadly, we may say that the nuclein is that constituent of the cell by virtue of which the histological unit grows, develops, and reproduces itself. It is the function of the nuclein of the cell to utilize the pabulum within its reach. It must be evident that those tissues most abounding in cellular elements contain relatively the largest amount of nuclein. It must also be seen that it is by virtue of their nuclein that the cells of various organs and organisms possess and manifest their individual peculiarities. We should, therefore, expect to find that the nuclein of the yeast cell is not identical with that of the bacillus tuberculosis, and that the nuclein of the spleen differs from that of the thymus gland. The number of kinds of nuclein is limited only by the variety of cells. Nuclein is the chemical basis of that part of the cell

[1] This paper contains the material used in special lectures delivered to the students of the Department of Medicine and Surgery of Michigan University, November, 1896.

designated by the histologist as the nucleus, sometimes called chromatin on account of the readiness with which it absorbs and holds coloring agents. It is the nuclein of the bacterium which takes up and retains stains, and it is on account of the fact that the nuclein of the bacillus tuberculosis differs from that of other bacilli that we are able to distinguish the former from the latter by its tinctorial properties. Differences in reaction with staining agents so plainly seen under the microscope are only outward manifestations of less apparent and more important differences in chemical composition.[1]''

Chemically, the nucleins are complex, proteid bodies, especially characterized by the large amount of phosphorus which they contain. Nucleins can be split up by the action of dilute mineral acids into albuminous bases and nucleinic acids. The nature of the base and the acid obtained in this way will vary with the nuclein in which they originate. Yeast nuclein differs in both its basic and its acid constituents from leuco-nuclein as obtained from the thymus gland. The nucleinic acids on being further broken up by the action of dilute mineral acids yield the so-called xanthin bodies, and here again it is true that the products obtained will depend upon the kind of nucleinic acid acted upon. One nucleinic acid may yield only adenin, and for this reason it may be designated as adenylic nucleinic acid, while another may furnish xanthin abundantly, possibly to the exclusion of other bases, and this may be termed xanthylic nucleinic acid. Kossel has demonstrated some

[1] The Nucleins and Nuclein Therapy; Annual Address on Medicine. Transactions of the Michigan State Medical Society, 1894.

of the chemical differences between nucleinic acids from diverse sources. Yeast nucleinic acid yields, on being broken up by the action of dilute mineral acids and heat, guanin and adenin ; while testicular nucleinic acid furnishes adenin, hypoxanthin, and xanthin ; and thymus nucleinic acid gives adenin only. These are what might be called gross differences. It is probable that finer distinctions exist between members of the same group. I have frequently observed that different samples of yeast vary not only in the amount of nucleinic acid yielded, but that the products differ in the intensity of their germicidal action. Of course this may be due to differences in other constituents of the yeast cells, and the greater or less difficulty of obtaining the nucleinic acid in an approximately pure condition. In the first year of my work on this subject I used baker's compressed yeast, and sometimes I wholly failed to obtain a nucleinic acid with distinct germicidal properties, while at other times the result was quite satisfactory, although at no time did I secure a product equal in germicidal strength to that subsequently prepared from pure cultures of brewer's yeast. It is within the range of possibility that by an investigation of the different varieties of yeast cells and with due attention to the conditions under which the cells are grown, we may secure not only a richer yield of nucleinic acid, but an acid of greater germicidal strength.

The difference in chemical composition and in germicidal action between nucleinic acids from different kinds of cells is, in some instances at least, accompanied by differences in physiological action.

Thus, while Lillienfeld[1] has found that thymus nucleinic acid coagulates the blood when injected intravenously in certain quantities, it will be shown in this paper that a much larger per cent. of yeast nucleinic acid may be injected intravenously without any such effects.

Certain substances which are histologically and functionally nucleins do not yield any xanthin base as a decomposition product. These are called paranucleins. Some of these are antecedents of true nucleins. Thus, the yelk of the egg contains a paranuclein, which may be isolated by removing the accompanying proteids by peptic digestion. This substance does not yield a xanthin base, but during the process of incubation it develops into a true nuclein.

Generally speaking, nucleins and nucleinic acids are insoluble in dilute acids and soluble in dilute alkalies. They are insoluble in alcohol. The last mentioned fact has not, however, prevented the quite extensive employment by the profession of alcohol said to contain nuclein. It is needless to say that any beneficial effects obtained by the use of this preparation should be attributed to alcohol and not to nuclein. The terms "nuclein" and "nucleinic acid" are frequently used interchangeably. In fact, it is by no means always easy to determine whether in a given kind of cell the nucleinic acid exists free or combined with some basic substance; and it is extremely difficult to obtain the nucleinic acid in any quantity wholly free from albuminous substances, and as nucleinic acid combines with any albuminous sub-

[1] *Ueber Blutgerinung Zeitschrift f. physiologische Chemie*, B. 20, S. 89.

stances present, the chemist is by no means always certain which of the terms "nuclein" or "nucleinic acid" will the more honestly fit a given product.

Pure yeast nucleinic acid contains about nine per cent. of phosphorus. While a small quantity can be prepared in a sufficiently pure state to yield this amount I have so far found the preparation of such a pure article in quantities large enough for any extensive physiological experimentation or therapeutical use impracticable. The purest nucleinic acid which has been used in the work detailed in this paper contains a fraction less than seven per cent. of phosphorus.

The Theory upon which these Studies of Nucleinic Acid have been Based.—The working hypothesis which I developed in beginning my researches on the nucleins, and which may be found in my address before the Medical Section of the first Pan-American Medical Congress,[1] may be condensed to the following propositions:

1. The phagocytic theory of Metschnikoff, in so far as it teaches that the polynuclear white blood-corpuscles are active agents in preventing or retarding the multiplication of pathogenic germs in the body, is true.

As Metschnikoff has stated, there is no claim that there are not other agents which may also combat the progress of disease.

2. The polynuclear corpuscles do not eat the bacilli, but they destroy the germ by virtue of the chemical action of some constituent or secretion.

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[1] "The Principles of Immunity and Cure in the Infectious Diseases." Transactions of the first Pan-American Medical Congress. Vol. 1, p. 152.

3. The germicidal properties of blood-serum, demonstrated by the researches of Fodor, Nutall, Buchner and others, are due to a substance, or to substances, that originate in the polynuclear white blood-corpuscles.

4. The natural resistance of the body to bacterial disease will be strengthened by a physiological increase in the production of polynuclear white blood-corpuscles.

5. This increase in the polynuclear corpuscles may be induced by introducing into the animal the most distinctive constituent of these cells, which is nuclein.

The foregoing statements were formulated in 1891 and I then began my studies on nuclein from yeast and from certain animal glands. In 1892 the first experiments were made on healthy and tuberculous guinea-pigs, and in May, 1893, tuberculous patients were treated for the first time with this agent.

The Germicidal Action of Nucleinic Acid.—In May, 1893, a paper by Novy, McClintock, and the writer,[1] detailed experiments by which we demonstrated the germicidal action of testicular, thyroid, and yeast nucleins upon bacillus venenosus, staphylococcus pyogenes aureus, and albus, and bacillus anthracis. Additional details of similar experiments were given in the address read before the Medical Section of the first Pan-American Medical Congress, already referred to. The paper by McClintock and myself[2] read before the same congress, demonstrated

[1] The Germicidal Properties of Nucleins. MEDICAL NEWS, May 30, 1893.

[2] "The Nature of the Germicidal Constituent of Blood-serum." Transactions of the first Pan-American Medical Congress. Vol. 1, p. 238.

that the germicidal properties of blood-serum are due to the presence of nuclein. In February, 1894, Kossel[1] published a paper which confirmed our results.

It is unnecessary to go into any detailed statement concerning the germicidal action of yeast nucleinic acid at this time, as any one desirous of doing so can consult the publications referred to. There is, however, one point which seems to me to be of special importance, in view of certain recent German investigations. While yeast nucleinic acid is a powerful germicide, it is not equally potent with all kinds of bacteria. Indeed, there are some germs on which this acid can scarcely be said to manifest a germicidal effect. This is true of certain putrefactive germs. This is of interest, in view of the discovery of Pfeiffer,[2] that the blood-serum of an animal, immunized against a specific bacterium, becomes decidedly more germicidal to that germ than to any other. This discovery is now being utilized in attempts to distinguish the typhoid and cholera bacilli from others which closely resemble them morphologically and tinctorially. It would seem from this that the germicidal constituent of the blood-serum can be trained to act more energetically upon a given bacillus. Pfeiffer states that the germicidal constituent of the blood-serum of his immunized animals is not a nuclein, and this makes the fact that yeast nu-

[1] "Weitere Beiträge zur Kentniss der Nucleinsäuren," *Archiv. f. Anatomie und Physiologie, Physiologische Abtheilung*, 1894, S. 194.

[2] "Ein Neues Grundgesetz der Immunität." *Deutsche med. Wochenschrift*, 1896, S. 97. Also, *Zeitschrift f. Hygiene und Infectionskrankheiten*, B. 20.

cleinic acid manifests its germicidal properties in a selective way all the more interesting.

The Effect of Treatment with Yeast Nucleinic Acid Upon the Polynuclear White Blood-Corpuscles.—As early as 1892, my colleague, Dr. Huber, kindly made for me a large number of counts of the white corpuscles in the blood of both healthy and tuberculous guinea-pigs, with and without injections of nuclein. He has since repeatedly made like determinations on the blood of my patients. I have elsewhere [1] stated his results, as follows:

(1) "The subcutaneous injection of nuclein increases the number of white blood corpuscles; (2) this increase occurs in both healthy and tuberculous persons; (3) with like quantities of nuclein injected, the increase varies with the person; it may be slight and it may be three-fold; (4) this increase occurs principally in the polynuclear cells; (5) it is evident, as a rule, as soon as the third hour after treatment, and generally disappears by the forty-eighth hour."

The following details of one series of counts may be of interest. All the persons tested in this series were tuberculous: [See next page.]

Recently Hahn,[2] working under the direction of Buchner, in the Hygienic Institute of the University of Munich, and using the nuclein prepared by Parke, Davis & Co., the same as that employed in the treatment of the cases reported in this paper, has gone one step further than I have in this investigation.

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[1] "The Nucleins and Nuclein-Therapy." Transactions of Mich. State Medical Society, 1894, p. 49.

[2] "Ueber die Steigerung der naturalischen Widerstandsfähigkeit durch Erzeugung von Hyperleukocytose." *Berliner klin. Wochenschrift*, September 28, 1896.

He has shown that nuclein not only causes a hyperleucocytosis, but that the defibrinated blood taken from the animal while in this condition of hyperleucocytosis, induced by the nuclein, has its germicidal properties increased. His experiments were made upon dogs, and are detailed as follows: "First, some blood was taken from the animal and the number of leucocytes in the arterial blood was determined. Then the animal received a hypodermic injection of some leucocytosis-producing substance. For this purpose, some albuminous body, as albu-

Patient.	Total No. of white corpuscles per c.m. before treatment.	Total No. of white corpuscles per c.m. after treatment.	Total increase per c.m.	Per cent. of increase.	Intervals between treatment and count.	Strength of nuclein solution used, per cent.	Amount of solution used.	Method of administration.
Miss B..	8421	12,395	3974	47+	3h. 45m.	1	3 i	h[1]
Miss F..	7617	13,866	6249	82+	2h. 45m.	1	"	"
Miss H..	4545	11,713	7188	158+	4h. 15m.	1	"	"
Mrs. R..	5000	11,578	6578	131+	3h. 10m.	1	"	"
Miss S...	9333	14,084	4751	50+	2h.	1	"	"
Mrs. D..	9564	10,947	1383	14+	3h.	5	3 iii	m[2]
Miss M..	5238	17,368	12,130	231+	2h. 30m.	5	"	"
Mr. M...	7520	10,138	2613	34+	2h. 30m.	5	3 ii	"
Miss A..	5977	8533	2556	44+	2h.	5	"	"
Mrs. N..	8713	12,959	4246	48+	2h. 30m.	5	"	"
Miss S...	8478	9189	711	8+	4h.	5	3 i	"
Mrs. R..	8441	9500	1059	12+	3h.	5	3 ii	"

[1] h=hypodermically. [2] m=by mouth.

mose or nuclein, the latter in the form of a yeast nuclein, supplied us by the firm of Parke, Davis & Co. A nucleinic acid from the same source has given

us good service. Since large quantities of this preparation can be employed, it was easy in a short time to double the number of leucocytes. At the same time, there was generally an elevation of temperature, which, with this agent, was variable. In dogs,

TABLE I.

STAPHYLOCOCCUS PYOGENES AUREUS.

		Number of Colonies on the Plates.					
		Immediately.	After 2 Hrs.		After 5 Hours.		After 24 Hours.
			Absolute.	Per cent.	Absolute.	Per cent.	
a	2 c.c. normal blood	6272	512	8.2	210	3.3	Innumerable
a1	2 c.c. normal blood	4992	1538	30.8	235	4.7	"
a2	Same as a & a1 heated to 55°.	6912	....	....	Innumerable	...	"
b	2 c.c. leucocyte blood ..	7744	194	2.5	89	1.1	7040
b1	2 c.c. leucocyte blood...	4096	139	3.4	94	2.3	Innumerable
b2	Same as b & b1 heated to 55°.	7552	8576	....	Innumerable	...	"

the elevation was seldom more than from 1° to 1½°. When the number of leucocytes had reached near the double of the normal, a second portion of blood was drawn. At first we allowed an interval of only from five to six hours, later, from twelve to fifteen hours between the injection and the withdrawal of the

second portion of blood. Even when the leucocytosis had begun to fall the results were not altered. The experimental proof that the leucocytosis was caused by the injection of the nucleinic acid was clear. The blood taken in the state of hyperleuco-

TABLE II.

BACTERIUM COLI.

		Number of Colonies on the Plates.					
		Immediately.	After 2 Hrs.		After 5 Hours.		After 24 Hours.
			Absolute.	Per cent.	Absolute.	Per cent.	
a	2 c.c. normal blood	3904	1664	42.6	256	6.6	Innumerable
a1	2 c.c. normal blood	4544	1792	39.6	384	8.5	"
a2	Same as a & a1 heated to 55°.	2112	5120	....	Innumerable	...	"
b	2 c.c. leucocyte blood...	3986	320	8.0	14	0.4	"
b1	2 c.c. leucocyte blood...	6080	1472	24.2	56	0.9	450
b2	Same as b & b1 heated to 55°.	7552	7680	....	Innumerable	...	Innumerable

cytosis was decidedly more markedly germicidal than the normal blood of the same animal. Control experiments, made morning and evening, without injection, demonstrated that the effect of the withdrawal of blood alone on an increase in the leucocytes was but small."

Table I illustrates the results obtained.

The results obtained by Hahn in a case of tuberculosis in man are shown in Table II.

Hahn states that in man the number of white corpuscles per c.m. must be increased to at least 13-1400 before there is any marked increase in the germicidal action. In one of my cases, not included in the table given, the number reached 45,000. This, however, was exceptional, and followed a very large injection. Moreover, it was a patient in the last stages of the disease, and with numerous cavities, as was demonstrated positively later at *post-mortem*, and Stein and Erbmann[1] have shown that in this condition there often exists a marked leucocytosis.

It must be admitted from the evidence before us that yeast nucleinic acid increases the number of polynuclear white blood-corpuscles. Hahn also found the increase to be among these elements, and that it intensifies the germicidal properties of the blood.

Is Yeast Nucleinic Acid an Antitoxin?—With our present knowledge of the infectious diseases, we may hope to find curative agents in one or the other of two classes—(1) those which increase the germicidal action of the blood, and (2) the antitoxins. Indeed, the infectious diseases may be divided into two groups, one of which includes those diseases which we may reasonably hope to cure by antitoxins, and the other those which must be reached by directly or indirectly destroying the germs. The diseases for which antitoxins have been found—diphtheria and

[1] "Zur Frage der Leucocytose bei tuberculösen Processen." *Deutsches Archiv. f. klin. med.*, B. 56, S. 323.

tetanus—are the best representatives, possibly the only members, of that class. Cholera and typhoid fever may finally be placed in the same group by the discovery of their antitoxins, but, in my opinion, this is not highly probable. In fact, the researches of Pfeiffer, already referred to, render it quite certain that cholera and typhoid fever are not to be combated successfully with antitoxins. The toxin diseases have the following characteristics:

(1) Their germs live in the animal body relatively only a short time; at least they manifest their virulence for only a short period. The bacillus of diphtheria may continue in the child's throat for weeks, but only for a few days does it manifest for that child any virulent activity. (2) The germs are located superficially on a mucous membrane or under the skin. (3) The germs are confined to relatively a very small area. (4) The tissue-changes induced by the growth of the germs are relatively of but little import. Diphtheria may cause death by filling the larynx with membrane, but this is not the usual cause of death in this disease, and, if it were, tracheotomy and intubation would save life. (5) Within a few days at most, the bacteria elaborate and pour into the body fatal doses of a chemical poison; then the bacteria cease, in that person, to manufacture more of the poisons. (6) These diseases are acute intoxications. The dangers to life, both those which are functional and those which are histological, are due to the chemical poison. The antitoxin does not destroy the germ, and the germ, after it has produced poison for a few days at most, is, for that individual, harmless.

The other group of diseases possesses the following distinguishing characteristics: (1) The germs may live and continue to manifest their virulence for a long time. The bacillus tuberculosis may slowly multiply and continue its existence in the same individual for many years. (2) The germs may be located either superficially or deeply; they may be confined to a small, or may extend over a large area. (3) Their germs elaborate chemical poisons for weeks, sometimes for years. An antitoxin would be possessed of no curative action in these diseases. It might be of temporary value, but the bacteria would continue to produce the poison. To cure these diseases, we must destroy the bacteria. All attempts to utilize chemical germicides in the curative treatment of disease have been failures. Our hope lies in the possibility of increasing the normal resistance of the animal body.

Then there are the acute septicemias—those diseases in which the germs multiply rapidly in the blood. In these also, curative agents will most likely be found in substances which either directly or indirectly destroy the bacteria.

Is yeast nucleinic acid an antitoxin? I think that I can answer this quite positively. McClintock and I have made a long series of experiments on rabbits and guinea-pigs with the toxins of diphtheria and tetanus and yeast nucleinic acid. We have failed to find any evidence that yeast nucleinic acid possesses any antidotal value against these toxins.

The Effect of the Administration of Nucleinic Acid on the Formation and Elimination of Uric Acid.—It was formerly supposed that uric acid resulted from the

retrograde metabolism of proteids in the same way as urea is produced. Uric acid was supposed to represent a condition of imperfect oxidation, the completed product of which is urea. On this theory, an excess of uric acid was supposed to indicate the administration of oxidizing agents directly or of those substances which would favor oxidation processes in the blood. It was upon the last-mentioned hypothesis that alkalies were so largely given when uric acid was formed in excess. However, Horbaczewski[1] has shown that the amount of uric acid is increased by the administration of nuclein. This fits in with certain chemical and physiological facts. As has already been stated, the xanthin bases are derivatives of nucleinic acid, and the close chemical, physiological, and pathological relation of uric acid to the xanthin bases is well known. The experiments of Horbaczewski would indicate that the administration of nuclein increases the number of polynuclear white corpuscles, and in the disintegration of these the xanthin bases and uric acid result. If this be true, uric acid becomes the measure, as it were, of cellular disintegration in the body. This theory has been combated with some vigor, mostly upon theoretical grounds, aided by a few experiments upon lower animals. However, the correctness of Horbaczewski's work has been confirmed by experiments made upon man by Weintraub[2] and others. My own observations are in accord with the teaching of Horbaczewski, and I have frequently found an excess of uric

[1] *Monatshefte f. Chemie*, 1889 and 1891.

[2] "Ueber den Einfluss des Nucleins der Nahrung auf die Harnsäurebildung," *Berliner klin. Wochenschrift*, 1895, S. 405.

acid in the urine after giving large doses of nucleinic acid. I have also, in persons suffering from rheumatic pains accompanied by the so-called uric acid diathesis, found that these pains were greatly intensified by the administration of nucleinic acid. In at least one instance was this so markedly true that the treatment was seriously interfered with and could not be given with the usual frequency. Cases of this nature are, however, judging from my experience, rare among the tuberculous.

Uric acid is not always increased in the urine after the administration of nuclein, but in all experiments on this point, in which proper tests have been made, it has been found that some one or more of the alloxan bodies is increased in amount. Uric acid is only one of the alloxan group, and failure to recognize this fact has led some writers into error which I cannot take the space to point out at this time.

Method of Administration.—In the cases reported in this and the preceding paper, the treatment has consisted of hypodermic injections. I use the syringe of a small aspirator, holding 80 minims. The barrel of the syringe should be long and of a relatively small diameter. The greater the diameter, the more difficult it is to discharge the contents through a fine needle. For the injection of larger amounts than that mentioned above, I have had a long-barrelled syringe, holding 10 c.cm., made. I select small needles, one for each patient, and keep the needles, when not in use, in an Esmarch dish filled with a five-per cent. solution of carbolic acid, and with the name of the patient on the cover. The syringe is kept, when not in use, in a covered glass dish such as is

used by bacteriologists, and known as a moist chamber. When the syringe and needle are kept in this way, no sterilization further than that due to the action of the carbolic acid on the needle is needed. The small amount of the acid adhering to the needle does no harm, and possibly may be of benefit, on account of its slight local anesthetic effect. When ready to give a treatment, some nuclein solution is poured into a clean Esmarch dish, the syringe is filled from this, and the needle is taken from its dish between the thumb and finger, touching only the base, and screwed upon the syringe. I prefer the American form of syringe, with the needle screwed on the barrel, to the German form, in which the needle is more loosely attached. The point of injection being selected, the skin is rubbed vigorously with a sponge wet with a five-per-cent. solution of carbolic acid. This rubbing should be well done, and is beneficial in two ways. In the first place, it secures cleanliness, not absolute sterilization, of the part, and, in the second place, the acid slightly anesthetizes the skin. Then, with a firm hand, the needle is introduced deep into the tissue. It is not well to pinch up a fold of the skin between the thumb and finger, as some do in the administration of morphin hypodermically, but with the thumb of the left hand on one side of the point of injection and the fingers of the same hand on the other side, press down and outward, making the skin tense at the point entered by the needle. Having introduced the needle, I inject the fluid very slowly. When the treatment is given in this manner, the pain is not nearly so great as that following the injection of an equal volume of dis-

tilled water, as I have frequently demonstrated. I generally inject in the infraclavicular areas, but the interscapular space is equally suitable. The subcutaneous injections should not be made in the arms, because there is not enough tissue, especially on the arms of many consumptives, to accommodate the fluid without painful distension. The injections may be made over the abdomen, on the buttocks, or in the thighs. In fact, they may be made on any part of the body or into any accessible area of mucous membrane. In the treatment of a case of lupus of the nose, I injected into the tissue immediately adjacent, but it was quite painful. In a case of local trouble in the upper portion of the vagina, I have injected through the mucous membrane after cleansing the point selected with a cotton swab saturated with the carbolic-acid solution.

The five- and ten-per-cent. solutions may be injected hypodermically, provided the reaction is not excessively acid or alkaline. When properly used, the stronger solutions cause no more pain than the weaker ones.

There is always more or less objection to hypodermic medication, especially when it must be continued for a long time. There are nervous patients who always dread the needle, and it is often inconvenient, sometimes quite impossible, for the physician to give the time to the treatment necessitated by the hypodermic method. I have fully realized these difficulties, and have given attention to the question of the absorption of nucleinic acid when administered by the mouth.

Since nuclein is separated from other albuminous

substances by digesting the latter with artificial gastric juice, it has been generally assumed that nuclein wholly escapes peptic digestion. Miescher first obtained nuclein in the residue left after the peptic digestion of pus corpuscles. However, since we have learned that the various nucleins differ so widely in many properties, this question has been re-investigated, with results that do not altogether confirm our previous knowledge. Popoff[1] digested a mixture of acid albumin and yeast nucleinic acid with pepsin-hydrochloric acid. The result was that a portion of the nucleinic acid remained in solution.

A like experiment was made on thymus. This gland, from a calf, was finely divided and separated into three unequal portions. The first portion, constituting about three-fifths of the weight of the entire gland, was digested for one hour with pepsin-hydrochloric acid. The mixture was then filtered, and the amount of phosphorus in both the residue and the filtrate determined after incineration with soda and saltpeter. The residue after extraction with alcohol and ether contained 2.56 per cent. of P. calculated for the dry substance, which weighed 35.5 grams and therefore contained 0.89 grams of P. The filtrate contained altogether 0.243 grams of P. This would indicate that not more than one-fourth of the P. of the thymus passed into solution.

A second portion, constituting about one-fifth of the gland, was submitted to like digestion for two

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[1] "Ueber die Einwirkung von Eiweissverdauenden Fermenten auf die Nucleinstoffe," *Zeitschrift f. Physiologische Chemie*, B. 18, S. 533.

hours. The result was that a greater quantity of the nuclein was thrown out of solution.

A third portion was digested for four hours. This resulted in the precipitation of a still larger per cent. of the nuclein.

Popoff found, however, that nucleinic acid is dissolved in the pancreatic juice.

Gumlich[1] has shown that the administration of nucleinic acid by the mouth is followed by marked increase in the phosphoric acid eliminated in the urine.

The statement of Horbaczewski[2] that the administration of nuclein increases the uric acid eliminated, has been repeatedly confirmed.

In our investigations, as has already been shown, yeast nucleinic acid given by the mouth increases the number of polynuclear white blood corpuscles.

These facts leave no room to doubt the absorption of nucleinic acid from the intestines. However, the dose by the mouth must be very much larger than that required to accomplish a like result given hypodermically. One cannot be certain in a given instance what proportion of that administered by the mouth is absorbed. For these reasons I regard the hypodermic method the more exact and otherwise preferable.

With care, nucleinic acid may be injected intravenously. I have at one time injected 5 c.cm. of a ten-per-cent. solution in this way without any bad results. Intravenous injections are painless, and theoretically this is the ideal method of administration,

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[1] "Ueber die Aufnahme der Nucleine in den thierischen Organismus," *Zeitschrift f. Physiologische Chemie*, B. 18, S. 508.

[2] *Monatshefte f. Chemie*, 1889 and 1891.

but a larger number of experiments must be made upon lower animals before the dangers in this method can be accurately measured. Therefore, I do not at present recommend it. I have elsewhere[1], with McClintock and Perkins, reported the employment of very large quantities of solutions of yeast nucleinic acid intravenously in rabbits, and have shown that with care this may be successfully done. Certainly, yeast nucleinic acid differs from leuconucleinic acid, inasmuch as the former does not coagulate the blood when injected intravenously.

Incompatibles.—Quinin and all the coal-tar antipyretics are to be avoided in the nuclein treatment. Atropin is probably physiologically antagonistic to the action of the nucleinic acids, and should not be given for night sweats in the nuclein treatment of tuberculosis.

Effect of Nuclein on Intestinal Fermentation.—Yeast nucleinic acid has a markedly retarding effect upon fermentation in the small intestines, as we have shown by determining its influence upon the conjugate acids eliminated in the urine.

THERAPEUTIC USES OF YEAST NUCLEINIC ACID.

Acute and Sub-Acute Inflammation of the Upper Air-passages.—I have used yeast nucleinic acid in the form of a spray with compressed air for nearly four years, in the treatment of acute inflammations of the upper air-passages as coryza, tonsillitis, pharyngitis, and non-specific laryngitis, and it has given me better results than any other form of medication I

[1] Transactions of the Association of American Physicians, 1896, p. 72.

have ever tried. I have employed for this purpose the one-per-cent. solution diluted with an equal volume of a saturated solution of boric acid. This preparation has also been of great service in the treatment of hay fever. It has not relieved all such cases, but it has given complete relief to some, has ameliorated others, and has failed to benefit but few. In hay fever, success is rendered more certain if, after spraying the nose, throat, and larynx thoroughly with the above-mentioned preparation, a small amount of a four-per-cent. solution of cocain be employed, also in the form of a spray.

Typhoid Fever.—The action of yeast nucleinic acid on fermentation in the small intestine induced me to try this agent in typhoid fever. I have had no opportunity to use it in any extensive epidemic of this disease. Dr. Harkin[2] of Marquette, Mich., has reported very favorably upon his results with the one-per-cent. solution in an epidemic of typhoid fever at that place. I have used it only in sporadic cases, and as these vary so widely in their clinical history I am not prepared to draw any conclusions from my experience. I think, however, that it is worthy of more extensive trial and would recommend for this purpose drachm doses of the five-per-cent. solution every two to four hours by the mouth.

In Cancer.—I have tried nucleinic acid in three cases of carcinoma of the breast. All of these had been submitted to operation, the cancer had returned, and the cases were inoperable. The treatment was, therefore, employed as a last resort. Injections were made into the healthy tissue around the growth.

[2] *Therapeutic Notes*, 1896, p. 30.

There was no evidence of beneficial action in any of these. I have employed similar treatment in two inoperable cases of epithelioma. There was no curative action in these. It is true that I did find a wash of nucleinic acid beneficial in these cases of epithelioma, inasmuch as it destroyed those germs which produced a most disagreeable stench. For this purpose I can commend a five- or ten-per-cent. solution as a wash for the diseased surface. In all of these cases, both of carcinoma and epithelioma, the growths were examined microscopically, and there was no doubt of the correctness of the diagnosis. In a case pronounced a sarcoma by some eminent specialists, nucleinic acid apparently wrought a marvelous cure. The patient, the wife of a prominent physician on the Pacific coast, was brought to her home near Ann Arbor in February, 1895, with what was pronounced a sarcoma of the pelvis. She was greatly reduced in weight and strength, weighing 73 pounds, and being unable to walk across the room. In fact, she was unable to sit up. There was a hard tumor, round and, as correctly as I could estimate, three inches in diameter, easily felt through the vagina, and apparently growing out from the ilium on the left side. The one-per-cent. solution of nucleinic acid was employed in the treatment which was administered by her husband. At first the injections were made directly into the growth through the walls of the vagina by means of a specially prepared needle. Later, the injections were made into the gluteal muscles. Treatment was given daily for six months, and then less frequently for some months longer. The strength and weight of the patient gradually increased, and the

size of the growth diminished *pari passu*. By the first of July, 1895, the patient weighed more than ever before, and she was able to walk several blocks. Her husband writes me as follows: "In January, 1896, there was some pain in the left side of the pelvis, and a small hardened mass appeared, quite tender and apparently occupying a fold of the broad ligament. Nuclein was used for about two months, injected into the gluteal region. By May, there was no sign of the trouble and an increase of weight was noticed, as well as an improvement of the general condition. At present writing (October 30, 1896) she weighs 123 pounds, which is about ten pounds more than she ever weighed. She is in good spirits and able to perform ordinary duties." Of course, this growth might not have been a sarcoma. The fact that it disappeared so completely is presumptive proof that it was not a malignant growth, but in a similar case I should certainly try the nuclein again.

Septicemia.—Boise[1] and Hofbauer[2] have reported good results from the treatment of puerperal septicemia with nuclein, the former using my preparation, and the latter that of Hobaczewski. Hofbauer states: "Among the clinical symptoms which were observed during the course of treatment, the following may be mentioned: (1) Effect on the general condition. This was manifested in a very marked and often surprising manner. Patients who previously lay apathetic and half asleep now give a clear and satisfactory answer when questioned as to their condition. Though

[1] "The Treatment of Puerperal Septicemia." Transactions of Mich. State Medical Society, 1896.

[2] *Centralblatt f. Gynœcologie*, 1896.

the temperature remained above the normal, nevertheless the improved appearance and the calm expression of countenance offered a decided contrast to what had previously been observed. At the same time the icteric tint of the skin disappeared, and the appetite was improved. (2) Influences on the local condition. Puerperal ulcers soon took on a healthy appearance and healed. The discharges from the septic uterus rapidly lost their odor and purulent character, and lessened in quantity. The first dose increased the temperature, followed by a gradual decrease. The remissions were longer and more pronounced, and the exacerbations slighter till restoration to the normal resulted.

TUBERCULOSIS.

The principal object in writing this paper is to continue the record of my experience in the treatment of tuberculosis with yeast nucleinic acid. Before taking up the report of cases I wish to make some inquiry concerning the curability of tuberculosis.

The incorrect ideas of Virchow concerning the pathology of tuberculosis, and the equally erroneous clinical teaching of Niemeyer concerning the malignancy of this disease, have been so deeply impressed upon the profession that, although more than thirty years have passed since Villemin laid the foundations of correct knowledge by the discovery of the transmissibility of the disease from man to animal, and from animal to animal by inoculation, the shadow of the older teaching still falls upon us. If I may be permitted to modify and condense one of

Cohnheim's statements on this point I should say: It happened fortunately that at the very time when Virchow was proclaiming the perfection of his teaching concerning the pathology of tuberculosis a discovery which was destined to prove his teaching erroneous was made in France.

Virchow attempted to make a sharp distinction between true tuberculosis and those processes in which caseation is, according to his teaching, due to inflammatory and hyperplastic processes. He taught that caseous pneumonia and scrofulous glands were not tubercular. The result of this teaching was that tuberculosis came to be regarded as a progressive process in which small malignant growths were formed, and which only exceptionally terminated otherwise than in death. Niemeyer founded his clinical teaching upon this pathology, and in doing so he employed statements more forcible in diction than true in fact, and these statements have not lost their influence upon the profession, although science has demonstrated their falsity. "The end of tuberculosis, as a rule, is death," is a statement which to-day largely determines the attitude of the medical profession towards the disease. "The greatest misfortune that can happen to one with phthisis is that he should become tubercular" is still practically repeated in much that is said about a "pretubercular" condition. The discovery of Villemin enabled investigators to demonstrate that the active virus in scrofulous glands, in granulation disease of the joints, in caries of the bones, and in caseous pneumonia is one and the same thing, and that susceptible animals inoculated with matter from any of

these sources become tuberculous. With this evidence before him the pathologist repeated his studies from a vantage point and the researches of Schüppel, Buhl, Ziegler, Senftleben, Cohnheim, Baumgarten, Köster, Friedlander, and others in Germany, and of Ranvier, Cornil, Grancher, Charcot, Lépine, Thaon, and others in France, completely demolished the pathology of tuberculosis as taught by Virchow and demonstrated the existence of tubercular lesions in parts of the body once supposed to be free from such invasion, such as the conjunctiva, the cornea, the choroid, the iris, the skin, the muscles, the bones, and the blood vessels. Finally, the discovery by Koch of the specific cause of tuberculosis has given positive proof of the etiological unity of its various manifestations.

The erroneous teachings of Virchow as to the pathology of tuberculosis have lost their force for all except the few who professionally live in the distant past; but the clinical teaching founded upon this false pathology, and as especially exemplified in the writings of Niemeyer, is still a controlling factor in our treatment of this disease. We have been too slow to perceive that our advanced knowledge of the etiology and pathology of this disease has given us just cause for a more hopeful attitude toward it.

In 1882, Baumgarten[1] wrote in sum and substance as follows: "Tuberculosis is in and of itself not so bad a disease. We do not believe that it possesses, as a constant property, 'the considerable local malignancy' which Friedländer believes he must still unconditionally attribute to it. When we see indi-

[1] *Ueber latente Tuberculose*, Volkmann's "Vorträge," No. 218.

viduals who as children had thickened, tuberculous cervical glands or tuberculous disease of the joints develop into the strongest and handsomest men; when we see people who in childhood had Pott's disease, which is always due to tuberculous caries of the vertebræ, live for years with this deformity, and reach advanced age; with such observations as these so frequently before us, we must conclude that tuberculosis is not so deadly as is usually supposed." . . . "The curability of phthisis pulmonalis was well known to the older pathologists. The distinguished Carswell wrote: 'In no other disease has pathological anatomy furnished more positive evidence of curability than it has for tuberculous disease of the lungs.' Under the dualistic theory, when a case recovered it was said to be one of simple inflammatory nature, and not tuberculous. However, since we know that caseous phthisis is tubercular, we must admit that tuberculosis is curable. The tendency to heal is much more evident in the 'true tuberculosis' of Virchow than it is in his caseous pneumonia. We will, therefore, come much nearer the truth if we take the oft-quoted saying of Niemeyer, 'The greatest misfortune which can happen to one with phthisis is that he should become tubercular,' and make it read as follows: 'The greatest misfortune which can happen to one with pulmonary tuberculosis is that he should become phthisical.'"

Tuberculosis, so long as it remains an unmixed infection, is not a deadly disease, and I believe it to be, in this stage, one of the most easily curable of the bacterial diseases. Except in the forms of acute miliary and meningeal tuberculosis, it is but seldom

the direct cause of death. However, as soon as it becomes a mixed infection, and is something more than tuberculosis, it then takes rank as the most fatal of all the diseases now afflicting mankind. In combating this disease, there are two points of attack, and if the wisdom and skill of the profession be directed to these, the death rate from tuberculosis will be much reduced in the near future. The first and most important method of dealing with this disease consists of the application of preventive measures. With these, however, I have at this time nothing to do. The second, the one with which I am now concerned, consists of the treatment of the disease while it remains an unmixed infection. When this is done, tuberculosis will cease to be "the terror of the laity and the cross of the physician." In order to accomplish this work, however, we must put aside certain dogmas, which we have so long mistaken for facts that their shadows frighten us. We must be convinced that as an unmixed infection it is curable. We must be able to recognize the disease while it remains an unmixed infection. We must cease regarding certain conditions as evidence of the existence of an indefinite, imaginary, so-called "pretubercular" state, and must learn to look upon these conditions as proof of the actual existence of tuberculosis. I will now give attention to these points, and in so doing I will consider them quite apart from the claims which I may make for nuclein or any other agent employed for curative purposes.

Is tuberculosis a curable disease? If so, to what extent is it curable? What shall we understand by "the curability of tuberculosis"? Are tubercular

deposits ever absorbed? Do such deposits ever wholly disappear and leave no trace of their former existence? May tissues once invaded by the bacillus tuberculosis regain histological continuity? Is there ever a *restitutio ad integrum*?

One-seventh of all men die of tuberculosis and one-third of all men have the disease. The first part of the preceding statement is shown to be true by the mortality statistics of all civilized countries. The second part of the same statement is shown to be true by the records of autopsies in various parts of the world. Massini[1] found evidence of tuberculosis as shown by scars, indurations, cheesy and chalky foci in eighty-nine out of 228 autopsies made upon persons who had died of diseases other than tuberculosis at the Basle Hospital. Müller[2] found in the Munich Pathological Institute that tuberculosis caused 29.4 per cent. of deaths in adults, and 30 per cent. in children, and that 11.8 per cent. more of the children had tuberculosis. Bollinger's[3] researches confirm these statements. Baumgarten[4] states that from one-fourth to one-third of all the bodies sectioned show tubercular lesions. Queyrat[5] found tuberculosis in 31.4 per cent. of the children examined. Lundonzy[6] reports that 30.4 per cent. of the children brought

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[1] As quoted by Hahn, "Ein Beitrag zu den Fieberverhältnissen bei der Phthise," S. 10.

[2] "Zur Kentniss der Kindertuberkulose." *Münchener Med. Wochenschrift*, 1889.

[3] "Ueber Entstehung und Heilbarkeit der Tuberkulose." *Münch. Med. Wochenschrift*, 1890.

[4] "Ueber latente Tuberkulose," Volkmann's "Beiträge," No. 218.

[5] "Sur la tuberculose infantile," *Progrès Médical*, 1896, p. 335.

[6] "De la frequence de la tuberculose au premier age." *Révue de Médicine*, 1887, p. 383.

to autopsy are tuberculous. Babes[1] found tubercular deposits in one-half the children dying from all diseases at Bucharest. In 1887 he sectioned ninty-three children, sixty-five of whom had tubercular glands. Haitnel[2] claims that one-third of the children examined at *L'hospice des Enfants assistés* show tubercular lesions. Simmonds, Schwer, and Boltz[3] state that autopsies at the Anatomical Institute at Kiel of 781 children, aged from one to five years, showed tubercular lesions in 230; of 228 between five and ten years, 78 were tubercular; of 162 between ten and fifteen years, 56. Wolff[4] states that autopsy reveals either recent or old tubercular lesions in from forty to fifty per cent. of adults and in from sixty to seventy per cent. of children; also that thirty per cent. of adults and forty per cent. of children have latent tuberculosis. Schlenker[5] found in 100 consecutive autopsies at Zurich 66 bodies tubercular; 35 of these had died of tuberculosis; in 4 others the disease was marked, but had not caused death; while in 27 it was latent and had not been suspected during life. In this examination no lesion was pronounced tubercular unless it was evident and characteristic to the unaided eye. He points out the fact that had the indurations been examined microscopically, the percentage of cases of latent tuberculosis would have been increased. According to Ados-

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[1] "Recherches sur les associations bacteriennes du bacilli de la tuberculose," *Progrès Méd. Roumain*, 1888.

[2] "La tuberculose héréditaire et la tuberculose du premier age."

[3] Quoted by Gartner. "Ueber die Erblichkeit der Tuberkulose," Zietschrift für Hygiene. B. 13, S. 132.

[4] *Deutsche Med. Wochenschrift*, 1892.

[5] "Beitäge zur Lehre von menschlichen Tuberculose." Berlin, 1893.

sides[1] of 4815 bodies sectioned at Halle from 1882 to the middle of 1893, 1066 showed gross tubercular lesions.

These and other statistics of like import justify the assertion that about one-third of all men are, at some period of life, infected with tuberculosis. Now, if one-third be infected and one-seventh die of the disease, it must be that the difference between one-third and one-seventh, a little more than one-fifth, are tubercular but do not die of this disease. Of the sixty-three millions of people living in the United States in 1890, nine millions have died or will die of tuberculosis, while twenty-one millions have been, are, or will be infected with the bacillus tuberculosis. Does this not demonstrate that tuberculosis does not possess the malignancy attributed to it?

The fact that one may be infected with tuberculosis and such infection remain localized for many years is shown by the study of cases of lupus. Out of 27 cases of lupus studied by Doutrelepont[2] the infection spread and the patient died of tubercular meningitis in only one instance. Hasland found 6 cases of what he regarded as metastatic involvement of the internal organs in 53 cases of lupus, and Holm[3] observed 11 in 62.

The study of instances of accidental inoculation with the bacillus of tuberculosis in wounds, some-

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[1] "Ueber den heutigen Stand der Therapie der Peritonis tuberculose," Halle, 1893.

[2] "Meningitis tuberculosa nach Lupus," *Deutsche Med. Wochenschrift*, 1886.

[3] Quoted by Schmidt, "Ein Fall von lokaler Impf-Tuberkulose der Haut."

times known as cadaver (Leichen) tuberculosis tends to similar results. It is true that the infection in these cases may extend to the internal organs, but often the disease remains a local infection and not infrequently a spontaneous cure occurs.

Verneuil [1] reports the case of an assistant who became inoculated at the root of a finger-nail while sectioning a tubercular body. Four or five days later a small point of suppuration appeared. Three years later the finger was amputated at the second phalanx and at the same time a tubercular abscess on the back of the hand was opened. Three years later still a bruise of the stump of the finger was followed by tubercular sequestration. Up to this time the internal organs had remained sound and subsequently the man died of spinal meningitis. Karg [2] reports the case of a physician who developed a wound tubercle on the thumb. For six years this remained without any signs of extension. Then the thumb became swollen and red and several tubercular abscesses developed along the lymphatics. These were opened and the bacillus found in the contents. Riehl [3] states that Dr. Karg inoculated himself in an interdigital fold. Two small tubercles were removed and found to contain bacilli. Kraske [4] observed a boy, who, after a surgical operation became infected from his tuberculous sister. The tuberculous growth was removed and the boy remained well. According

[1] *Sémaine Médicale*, 1885.
[2] "Tuberkelbacillen in einem sogenanten Leichentuberkel." *Centralblatt für Chirurgie*, B. 12.
[3] "Tuberkelbacillen in Leichentuberkel." *Centralblatt für Chirurgie*, B. 12.
[4] "Ueber tuberkulose Erkrankung von Wunden." *Ibid.*

to Tscherning [1] a servant inoculated her finger with the broken cuspidor of her tuberculous master. The tubercle at the point of inoculation and some swollen axillary glands were removed and in these the bacilli were found. The servant remained in good health. Lehmann [2] observed ten Jewish children with local tuberculosis after circumcision by a tuberculous rabbi. Three died of marasmus, three of tubercular meningitis, one of intercurrent diphtheria, and three recovered. Many other cases of wound tuberculosis have been reported and a valuable review of the subject has been written by Schmidt.[3] The study of these cases shows that inoculation with the bacillus tuberculosis does not always cause death, and that man is much less susceptible to the disease, when thus acquired, than are rabbits and guinea-pigs.

Further evidence that one infected with tuberculosis may recover from the disease is furnished in the observation of other forms of local tuberculosis. Tuberculous joints often heal, and the child afflicted in this way may develop into the most robust adult. König[4] says that coxitis may heal at any stage of the disease. Tubercular abscesses may disappear and leave scar tissue as the only evidence of their existence. Tubercular orchitis and tubercular pericarditis have been known to disappear. These evidences of the possibility of the healing of tissue once invaded with tubercles should encourage us, because in

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[1] "Inokulationtuberkulose beim Menschen," *Fortschritte der Medicin*, 1886.

[2] "Ueber einen Modus der Impftuberkulose," *Deutsche Med. Wochenschrift*, 1886.

[3] "Ein Fall von lokaler Tuberkulose der Haut."

[4] *Specialle Chirurgie*, B. 3, S. 445.

all cases tuberculosis begins as a local disease, and the tissue at first involved is only of microscopic extent. The germ is inhaled, and finds lodgment, and begins to multiply somewhere in the lung. The sooner the inoculation is recognized the greater are the chances of so improving the resistance of the tissue that extension of the infecting agent does not occur, and then it dies out or remains localized. I have stated that every case of tuberculosis begins as a local disease. The researches of Buhl and others have shown that this is true even in acute miliary tuberculosis and in tubercular meningitis. In these the systemic infection comes from a pre-existing tubercular focus. Friedlander[1] and others have described quite thoroughly the changes which take place in the spontaneous healing of local tuberculosis.

The evidence that tuberculosis of the peritoneum occasionally undergoes a spontaneous cure and frequently heals after laparotomy is no longer questionable.

Since the publication of the now classical paper by König[2] in 1884, on laparotomy in peritoneal tuberculosis, surgeons in every part of the world have resorted to this operation as a curative agent, with a fair degree of success. These cases have been collected and the results summed up by Phillips,[3] Lauser,[4] and others.

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[1] "Ueber locale Tuberkulose," Volkmann's *Vorträge* No. 64.

[2] *Centralblatt für Chirurgie*, 1884.

[3] Die Resultate operation Behandlung der Bauchfell tuberkulose. *Gekrönte Preisschrift*, Göttingen, 1890.

[4] Ueber Tuberkulose-Peritonitis und ihre Behandlung durch Laparotomie. Regensburg, 1893.

Adossides [1] has tabulated 405 laparotomies for tubercular peritonitis with thirteen per cent. of cures, counting as cured all those who lived two years or longer after operation.

It will be interesting to learn, so far as we are able, the histological changes involved in these cases of cure of tubercular peritonitis after operation. Is there a complete disappearance of the tubercles? Richelot[2] opened the abdominal cavity on account of strangulated hernia in a woman upon whom he had twice before performed laparotomy for tubercular peritonitis. The last operation for tuberculosis had been made one year before that for the hernia. He found the peritoneum perfectly smooth, of normal color, and free from adhesions. Knaggs[3] performed laparotomy for tuberculosis, and five and one-half years later operated on the same woman for hernia. At the second operation there was no trace of tuberculosis detectable, although at first the intestines, mesentery, and parietal peritoneum were thickly covered with tubercles. Clarke [4] reports a case in which an ovariotomy was made eighteen months after a laparotomy for tubercular peritonitis, and the second operation showed that the tubercles had wholly disappeared. Similar cases with similar findings have been reported by Schede, Winiwater, Ahlfeld, Hirschberg, Schmalfuss, Tait, Feldmann, Terillon, Esmarch and Werth (see monograph by Adossides).

These observations demonstrate not only that tu-

[1] "Ueber den heutigen Stand der Therapie der Peritonitis tuberculosa," Halle, 1893.
[2] *Revue de Chirurgie*, 1893.
[3] *Lancet*, November 11, 1892.
[4] *Ibid.*

bercular peritonitis may be cured by laparotomy, but that the cure may mean a complete *restitutio ad integrum*.

The following experiments bear upon this point: On December 31, 1895, we inoculated three full-grown rabbits intra-abdominally with a pure culture of the bacillus tuberculosis. No. 1 was employed as a control, and received no treatment of any kind. It died May 25, 1896. The peritoneum, omentum, liver, and spleen were tuberculous. There was also a large tubercular abscess in the abdominal wall at the point of inoculation.

No. 2 was placed in the holder January 25, 1896, and the abdominal cavity opened. In the wall at the place of inoculation there was a tubercular induration as large as a nickel. In the mesenteric fold of the colon there was a tubercle as large as a pin-head and many smaller ones. The omentum was filled with small nodules, and the border of the liver was dotted with pin-point tubercles. After noting these facts, the abdomen was closed and nothing more was done to this animal until July 24, 1896, when it was killed. What had been a tubercular induration in the wall was at the autopsy only a lump of yellow fat. No sign of tubercle could be found in it. The liver was perfectly sound. There were heavy deposits of fat of a deep yellow color in the omentum and mesentery, and in these the tubercles observed at the time of the laparotomy were found. These nodules had not increased in size, but they contained a caseous center in which tubercle bacilli, which stained normally, were found.

No. 3 had its abdominal cavity opened January

25, 1896. There was an induration in the wall a the point of inoculation similar in size and appearance to that observed in No. 2. The mesentery and omentum were filled with nodules the size of flax-seed and the border of the liver dotted with fine tubercles. One nodule was cut from the omentum and examined for bacilli, which were abundantly present. The abdomen was closed, and 45 c.c. of a one-half per cent. solution of nucleinic acid was injected into the jugular vein. Nothing further was done to this animal until July 24, 1896, when it was killed. Not the slightest evidence of tubercle could be found anywhere. The induration in the wall had wholly disappeared and the mesentery and omentum were perfectly smooth. The deposits of yellowish fat observed in No. 2 were not found.

The following details will show that the skin and muscles may also regain histological continuity after tubercular invasion. November 18, 1895, two rabbits, which may be designated as A and B, were inoculated intra-abdominally with tuberculous sputum. The weight of A was 1552 and that of B 1402 grams. On December 6, 1895, A died. There was a caseous infiltration extending for one and one-half inches longitudinally and one-fourth inch transversely under the skin of the abdomen. The muscles of the abdomen were infiltrated with a creamy, semi-solid exudate, in which the diplococcus pneumoniæ, in great numbers, and the bacillus tuberculosis, in small numbers, were found. There was some effusion in the peritoneal cavity, and in this also both the above-mentioned germs were present. Death was due to the septicemia induced

by the diplococcus. At this time B showed a suppurating sore two inches in length and one-fourth inch broad on the abdomen, and a round ulcer three-fourths of an inch in diameter and extending deep into the muscles on the right thigh. Tubercle bacilli were repeatedly found in the pus from each of these sores. December 6, 1895, 50 c.c. of a one per cent. solution of nucleinic acid was injected into the jugular vein and the next day 15 c.c. more was injected into the vein of the ear. On December 7 B weighed 1394 grams, on December 14, 1480, and on December 21, 1592. On December 27, B was found to be losing in weight, falling to 1542 grams. At this time the sore on the abdomen had healed over, but a nodule had appeared at the point of inoculation and had grown to the size of a filbert. The sore on the hip was still discharging, although it had decreased very much in size. On December 27, 1895, B received hypodermically about the nodule on the abdomen 30 c.c. of the one per cent. solution, and two days later 40 c.c. more. After this B received no further treatment, but continued to grow fat and strong. On July 23, 1896, B was killed; weight at that time was 2030 grams. There was some adhesion of the skin to the muscles over the abdomen where the sore had been, but nothing more. The hard nodules had wholly disappeared. All internal organs were in perfectly normal condition. The ulcer on the hip had wholly disappeared and there had been complete reconstruction of the injured tissues. There was not even a scar to mark the place of the former lesion.

I have brought forward these observations on the

rabbits at this time not for the purpose of making any claims for nuclein, but in order to show that there may be a *restitutio ad integrum* in tissue after tubercular invasion. For my present purpose it matters not what be the nature of the agent that brings about the restitution.

Many theories have been advanced to explain the curative effect of laparotomy on tubercular peritonitis. It has been attributed to the influence of the light, which reaches the peritoneum during the operation (Lauenstein), to the entrance of air (Mosetig-Moorof), to mechanical irritation and the presence of air (Caspersohn), to the bacterium termo, which is supposed to enter the cavity with the air (Cantani), to a digestive action of the peritoneum, that is assumed to be called into action by ths operation (Sänger), to a suction action, "aufsaugende kraft" of the peritoneum, due to the relief of pressure (Fritsch), to the oxygen of the air (Braatz), to improved resorption (Lindner), to inflammatory adhesions (König, Breisky, Hartman, and Aldibert), to a connective tissue reaction (Phillips), to improved circulatory and respirating action, and to relief of the autointoxication (Vierordt), and to the use of disinfectants used in the operation and sometimes in washing out the cavity (Preindlsberger and Ceccherelli). However, the explanation suggested by Kischenski[1] that the cure is due to the leucocytosis which follows the operation is the most reasonable. Adossides accepts this explanation and sensibly adds that the action of the leucocytes is favored by (1) the relatively small number of bacilli present, and

[1] *Centralblatt für Chirurgie*, 1893.

(2) the great extent of the peritoneal membrane and its great vascularity.

Tubercular peritonitis has been cured not only by surgical means, but under medicinal treatment also. Such cases have been reported by Bouilard, Vierordt, Anderson, Comby, Fagge, and others.

Cases of tubercular meningitis terminating in recovery have been reported, but from the nature of the disease it is difficult to furnish positive evidence to this effect. However, such able diagnosticians as Rilliet and Trosseau have reported cures. I have carefully studied the monograph by Zwicke[1] on this subject, and must conclude that he does not supply convincing proof of the correctness of his diagnosis in the case of cure reported by himself.

The researches of Orth,[2] Fraenkel,[3] and Progn-binsky[4] have demonstrated that tuberculosis may be located primarily and exclusively in the larynx, and Schmidt[5] claims to have cured five cases of this disease by tracheotomy. He attributes the curative action to the rest given the larynx and to the more direct action of the oxygen of the air. Glöckner[6] has reported two cases treated by tracheotomy without benefit, but in both of these the lungs were extensively involved and the ulceration of the larynx was probably secondary; certainly the disease was not

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[1] "Beitrag zur Heilung der Meningitis basilaris tuberculosa," Bonn, 1868.

[2] "Lerhbuch der Patholog. Anatomie."

[3] Primare Kehlhopftuberkulose. *Deutsche Med. Wochenschrift*, 1883, S. 490.

[4] *Medycyna*, 1887.

[5] *Deutsche Med. Wochenschrift*, 1885 and 1886.

[6] "Ein Beitrag zur Behandlung der Laryngo-Phthisis tuberculosa," 1890.

confined to the larynx. Krause[1] has claimed success in the treatment of laryngeal tuberculosis by his method, with lactic acid, and his observations have been confirmed by von Schroetter,[2] Keimer,[3] Heryny,[4] Jellinick,[5] and others. Like good results are claimed for iodoform by Beschorner,[6] Schultzer,[7] and others.

In regard to the cure of pulmonary tuberculosis, either spontaneously or under climatic or medicinal treatment, there is much information to be found in medical literature, but it can not be so positive as that given concerning peritoneal tuberculosis. If there be histological restoration there can be no evidence after death of the existence of the disease during life. Scars and chalky deposits are frequently observed, and the fact that these contain tubercle bacilli demonstrates the former existence of the disease in an active form. Carswell[8] states, as has already been quoted, "that pathological anatomy has probably not given such positive proof of the curability of any other disease as it has of phthisis." Weber[9] says: "It seems to me impossible for any one acquainted with the literature of the subject to

[1] "Milchsaure gegen Larynxtuberkulose," *Berlin Med. Wochenschrift*, 1885, and *Deutsche Med. Wochen.*, 1886.

[2] "Verlosungen über die Krankheiten des Kehlkopfe."

[3] "Ueber Kehlkopftuberculose, ihre Behandlung und Heilung." *Deutsche Med. Wochenschrift*, 1886.

[4] *Deutsche Med. Wochenschrift*, 1886.

[5] "Ueber Milchsaurebehandlung im Kehlkopf, Rachen und der Nasse, Centralblatt für die gesamte Therapie."

[6] "Die localer Behandlung der Laryngo-Phthiso-tuberculosa," Dresden, 1888.

[7] Ueber Diagnose und Heilbarkeit der Kehlkopfschwindsucht unter dem Einflusse des Iodoforms *Wiener Med. Presse*, 1882.

[8] *Pathological Anatomy*, London, 1838.

[9] "Lectures on the Hygienic and Climatic Treatment of Chronic Pulmonary Phthisis" (German edition), Leipzig, 1888.

doubt the curability of phthisis." Rühle[1] asserts that tuberculous processes in the lungs may heal.

Green[2] says: "It lies in the very nature of the case that there can be no absolute cure, no *restitutio ad integrum*, and the very best that can happen is the formation of a scar or of a chalky deposit."

"One frequently has the opportunity of seeing these healed foci in various stages; sometimes as scars, again as connective tissue nodules, or as cavities filled with chalky concretions. The size of these cavities varies from that of a hemp seed to that of a hazelnut. Generally the remainder of the lung is in a normal condition. These healed places are generally found in the apices, where tuberculosis most frequently begins. They lie near the surface; the apex is more or less contracted; the pleura pulmonalis is thickened and more or less adherent to the pleura costalis. To the finger these points feel like hard lumps. The interior of the nodule consists of a well encapsuled mass of variable consistency depending upon the length of continuance of the healing process. The center is hard, generally calcified, while the periphery is softer, incompletely calcified."

Green has examined a number of these healed cavities microscopically and in some the bacilli were detected, while in others the result was negative. Dejerine[3] has made a similar study with like results. He also inoculated guinea-pigs with the wholly calcified material and failed to induce tuberculosis.

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[1] Ziemssen's *Handbuch*.

[2] *Ueber Tuberkelbacillen in alten ausgeheilten Lungenherden*, Berlin, 1889.

[3] Recherche des bacilles dans la tuberculose calcifiée et caseo-calcifiée, *Revue de Médicine*, 1884.

Kurlow[1] obtained the following results from his inoculations:

1. Using scar nodules in which no bacilli could be found; two inoculations; both negative.

2. Using completely calcified nodules in which no bacilli could be found; four inoculations; all negative.

3. With caseo-chalky nodules about which no tubercles could be found. In many of these nodules no bacilli could be detected; twelve inoculations; all the animals became tuberculous.

4. With caseo-chalky material about which tubercles were found; seven inoculations with positive results in all.

Nauwerk,[2] Demme,[3] and others, have given the clinical histories of cases of recovery from pulmonary tuberculosis with death from some other disease and the findings at autopsy.

Wolff and Saugmann[4] have given us valuable information concerning the possible cure of pulmonary tuberculosis. In 1862 Brehmer began the treatment of tuberculosis in his hospital at Görbersdorf. In 1890 Wolff and Saugmann sought out many of the earlier cases treated by Brehmer, and reported upon their condition. The number found and studied was 142. In some of these the evidence of the previous existence of the disease and its arrest cannot be

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[1] Ueber die Heilbarkeit der Lungentuberkulose, *Deutsches Archiv. für klin. Med.*, B. 44.

[2] "En Fall von geheilter Lungentuberkulose," *Deutsche Med. Wochenschrift*, 1883.

[3] "Jahresbericht über die Thatigkeit des Jennerschen Kinderhospital in Bern," 1884.

[4] "Ueber Dauerende Heilung der Lungentuberkulose," Wiesbaden, 1891.

doubted. One of these is reported as follows: In 1876, a woman entered Brehmer's hospital with infiltration of the right lung to the third rib, and a less marked infiltration over the same area of the left lung. She had fever and night sweats, and was reduced in flesh. She remained in the institution thirteen months, and was dismissed "cured." Fourteen years later she was operated upon for myomata uteri and died. A few days before death her lungs were carefully examined, and the only evidence of disease that could be found was a slight prolongation of the expiratory sound over the upper right lung. Section showed a cicatricial contraction, with a circumference of about 4 cm. in the right apex; otherwise no abnormality could be found in the lungs and no tuberculosis in any part of the body. In microscopical sections of the scar tissue tubercle bacilli, which stained well, were found. The authors are certainly justified in the conclusion drawn from the case. Considering the severity of the case when it came under treatment, fourteen years before, the cure must be regarded as ideal, but, nevertheless, it was not absolute, because the bacilli remained and, as indicated by the tinctorial reaction, retained their vitality, and in this respect the patient showed a condition no more serious than that exhibited by "one-half, or at least one-third, the bodies that reach the autopsy table."

These authors conclude that at least eight per cent. of those treated at Görbersdorf from 1862 to 1891 were permanently cured.

I have gone into the question of the curability of tuberculosis thus specifically (and I might say that

the evidence on each point might be confirmed more fully did space and time permit) because I believe that the present attitude of the profession in general toward this disease is radically wrong and harmful. I believe that I am right in saying that the average physician does not strive to recognize this disease as early as is possible, but that he wilfully disregards all evidence of its existence until, in the majority of instances, it is altogether too late. I shall have something to say concerning the means of an early diagnosis in another part of this paper.

I will now proceed to state the results obtained in the treatment of tuberculosis with yeast nucleinic acid. In doing this I will make the reports of cases as short as is possible, and at the same time consistent with clearness. In order to avoid repetition, I may state here that in all of the seventy-five cases reported the tubercle bacilli were found; and in all of the urinary cases guinea-pigs were inoculated and tuberculosis developed, in order to be certain that I had not mistaken the smegma bacillus for that of tuberculosis. No case is reported in this list which first came under observation later than December, 1895.

Review of Cases Reported in 1894.—Two years ago I reported twenty-four cases treated with yeast nucleinic acid.[1] At the time of that report twelve of these patients were living. It will certainly be of interest to give the further history of these cases, and this I will now proceed to do as briefly as is consistent with accuracy.

[1] "Treatment of Tuberculosis with Yeast Nuclein," MEDICAL NEWS, 1894.

CASE II.[1]—I began treating this young man May 1, 1893. At that time "moist râles were heard over both lungs, both anteriorly and posteriorly. No cavities could be detected. The sputum contained numerous tubercles, which on being crushed and stained were found to be filled with bacilli. The daily maximum temperature for three days before beginning the treatment averaged 100.3° F. Night sweats were constant."

The treatment was continued through May and June of 1893. "The temperature did not reach 100° F. after June 2d; it seldom went higher than 99° F., and during the last four days of treatment it was normal continuously. Night sweats were occasional and slight during June. The cough and expectoration decreased, and some mornings during the latter part of June, he failed to raise anything when asked to bring the sputum for examination; but when the sputum was raised and examined the bacillus was always found."

In July, 1893, this young man went, by my advice, in a wagon from Kansas City to Boulder, Col., where he has continued his residence. He has had no medicinal treatment since going to Colorado. He considers himself well, but his weight is practically the same as it was when he was under treatment in 1893, and the sputum, a little of which is coughed up nearly every morning, contains from two to six bacilli in each field. I have not seen the patient since June, 1894, when a physical examination showed practically the same condition of the lung as that existing one year before, and consisting wholly of diminished resonance over both upper lobes.

From this case, I have drawn the following conclusions, subject of course, to revision, as all such conclusions must be, by future observations: (1)

[1] Refers to number of case in first report.

Physical examination of the lungs in tuberculosis shortly after a hemorrhage (this patient had a hemorrhage the day before the first examination) may give a very erroneous impression of the extent of the involvement. The moist râles heard over the greater portion of both lungs in the first examination of this case were due to the pneumonic infiltration induced by the hemorrhage, and the area of tubercular involvement was not so great as I at first supposed. (2) The sputum may contain tubercle bacilli long after the patient supposes himself well. This is certainly true when the disease has been arrested by residence in a favorable climate. This explains the frequently observed fact that consumptives apparently cured by long residence in a suitable climate suddenly develop an active and rapidly progressive form of the disease on returning to a less favorable climate; or the equally well known fact that such persons may remain in apparent health so long as they live out of doors, but soon die of tuberculosis on changing their occupation to one more sedentary, especially when a large portion of the time is spent under unsanitary local conditions.

Webber[1] gives the following interesting history of a tubercular family, which suggests the possibility of the tubercle bacillus remaining in an inactive state in the body for many years:

"Thirty years ago I treated a woman in a small street in Bloomsbury Square for galloping consumption. Her husband, a teacher of languages, had died shortly before, at the age of thirty-eight, in the German hospital, of chronic tuberculosis. Both his and her family were tuberculous.

[1] "Lectures on the hygiene and climatic treatment of chronic pulmonary phthisis" (German translation), p. 31.

They had seven children, one of which had already died of tuberculosis. Of the six remaining children all save the youngest, a rachitic boy, were apparently healthy. On the death of the mother, intelligent and well-to-do friends took the children to one of the most healthful parts of Germany and brought them up under the best hygienic conditions. The eldest son remained perfectly well so long as he lived out of doors, but at the age of twenty-three he became deeply interested in philological studies and worked day and night, confining himself to his study-room, in which he took most of his meals. Eighteen months later he died of quick consumption. The second son interested himself in agriculture until he reached the age of twenty-nine. Up to this time he apparently enjoyed perfect health. At the above-mentioned age he changed his occupation, and worked in an office, confining himself closely. Two years later he began to have hemorrhages and ultimately died of tuberculosis. The third son entered and continued in a cavalry regiment, and is the picture of health. The fourth child, a girl of five years of age at the time of the death of her mother, is now the healthy wife of a German farmer. The youngest son, the rachitic boy, is now a robust farmer in Manitoba, and the youngest daughter, also in perfect health, lives with her Canadian brother."

Of course it is possible that the first and second sons might have become infected for the first time after entering upon their sedentary occupations, but it is also possible that they might have carried the infection from their early childhood. The presence of living tubercle bacilli in calcified cavities in the lungs is mentioned in another part of this paper. The point which I wish to emphasize here is that one in apparent health may carry the tubercle bacillus in his lungs for many years.

Under date of November 1, 1896, this patient (Case II) writes me as follows: "I have examined my sputum and find b. tuberculosis in it in such

small numbers that in a cover-glass preparation it takes a little hunting to find them. My general health is excellent. I spent the summer out of doors and climbed Long's Peak (14,270 feet) without difficulty."

CASE IV.—This was an aggravated case of urinary tuberculosis. Hypodermic injections of iodin and gold, and boric acid, salol, quinin and iodoform by the mouth, had been tried. One gallon of cod-liver oil was taken within seven weeks. The nuclein solution was administered hypodermically and also injected into the bladder. This treatment was begun in June, 1893, and continued for nearly one year. In November, 1894, the patient, a practitioner in Nebraska, reported no incontinence, scarcely any irritation of the bladder, and that he weighed more than he had for twelve years. No bacilli could be found in the urine. In March, 1896, he wrote me that he remained free from any evidence of a return of the disease, and that he had been engaged in a very laborious country practice. January, 1897, he reported himself as being perfectly well.

CASE V.—This was also a case of urinary tuberculosis of several years' duration. I closed my report on this case in 1894 with the following paragraph:

"The greatest weight reached before the illness was 132 pounds. The decrease was gradual and constant to the time of beginning the treatment, when he weighed 114 pounds. Since that time there has been a steady increase, and the figure is now 138. The temperature at first often reached 102.5° F., sometimes 103° F. It has not been above the normal since early in October, 1894. The urine will be wholly free from sediment for several consecutive days, and then there will be a little pus in which the bacilli can be detected. There is still some undue fre-

quency of micturition, and at times a sensation that the bladder has not been wholly emptied at the close of this act. The kidney has decreased in size, but is still abnormally large. There has been no pain from the passage of tuberculous masses through the ureter since the latter part of May, 1894. *Of course it is possible that the disease may extend again. I shall not call this a cure until the urine becomes permanently normal, and this may never happen.* But even should this not occur, the history of the case is unique."

The wisdom of the caution expressed in the sentences now italicized soon became evident. In the spring of 1895, this young man, notwithstanding the continued use of the nuclein, developed acute general miliary tuberculosis and, although he hastened to Colorado, died within a few months. This is the most marked case of the temporary abatement and subsequent rapid spread of the disease under the continued employment of the nuclein that has fallen under my observation. The remedy lost completely its apparent value, and was wholly without effect. This case illustrates the relation between local and acute miliary tuberculosis and the inadequacy of the nuclein treatment in the latter.

Case VI.—This, the third case of urinary tuberculosis reported in my article of 1894, has continued without any evidence of the existence of the disease. Dr. R. remains well, is engaged in a laborious practice, and one year ago published an interesting report of his own case.[1]

Case XVII.—This man continued this treatment until February, 1895. I last saw him in June, 1895.

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[1] *Therapeutic Gazette*, October 15, 1895.

At that time there was still a marked prolongation of the expiratory sounds over both upper lobes, and the afternoon temperature generally registered 99° F. His weight remained at 140 pounds, and he raised some sputum each morning, which contained a few bacilli. Since June, 1895, I have not been able to ascertain his residence, and consequently have no knowledge of his present condition. The conclusion concerning this case, as stated in my report of 1894, was as follows: "I believe that in this case the disease has been retarded by the treatment—I will not say arrested, because so long as the infection remains there also remains the probability that it may at any time become progressive."

As this was a colored man, living from "hand to mouth," I shall expect should I hear from him again, that the disease has progressed.

CASE XVIII.—This was a patient with a cavity in the upper lobe of the right lung and an extensive tuberculous pleurisy on the opposite side. Germs were abundant in the sputum and some were present in the effusion drawn with a needle from the left side. Treatment was begun February 19, 1894, and continued to November 23d of the same year. During this time the young man continued his work as bookkeeper and general office boy, cleaning the rooms, etc., in a bank. The weight practically remained unchanged during treatment but the average temperature slightly increased and "judging by this more than by the physical signs, I think that the disease is slowly progressing." A few days after discontinuing this treatment the young man went to Colorado, but the progress of the disease continued and he died in September, 1895.

CASE XIX.—This is a saleswoman in a dry-goods store. The weight had fallen from 148 to 115 at the time of beginning the treatment, January, 1894. There was bronchial breathing over the right apex

and subclavicular area and moist râles over the upper lobe of the left side. "*The sputum was non-purulent but contained tubercle bacilli.*" The treatment was begun January 4, 1894, and continued daily until the middle of July of the same year, when it was given twice a week until the first of October, 1894, and then once a week until June, 1895, since which time no nuclein has been given. The germs disappeared in March, 1894, and whenever on account of cold there has been any sputum, it has been examined, always with negative results. The patient continues her duties as a saleswoman and the conditions under which she lives are highly unfavorable. It is of interest to state that she is the third among the women clerks in the same store known to have developed consumption in the past six years. I have recently examined her lungs and fail to find any evidence of disease. Her weight varies from 125 to 135 pounds. This I have regarded as practically a case of unmixed infection. For two and one-half years the germs have not been found.

Case XX.—In the report of 1894 I stated that in this case the tubercle bacilli had not been found in the sputum since the last of March of that year, but that the tubercular cervical glands remained enlarged. This young lady continued under my charge until May, 1895. At that time her condition remained the same practically as stated in my last report. About this time her betrothed died very suddenly of appendicitis and since then the young lady has refused to take further treatment. Shortly after this I was called to see her on account of a pulmonary hemorrhage. I have examined the sputum and the blood and found the bacilli. She has been to my office a few times since and I have examined her lungs. The disease is slowly progressing. She still refuses further treatment.

Case XXI.—I last examined Mrs. M. in Septem-

ber, 1895. At that time there was no evidence of any disease in the lungs. She had no cough, and was, so far as I could ascertain, in good health. I have not seen her since that time, but she remains apparently well, and wholly free from cough.

Case XXII.—In this case the sputum was abundant, but non-purulent, and contained only a few bacilli. The bacilli disappeared in July, 1894, and none have been found since. Mrs. R. has borne one child since my last report. Her weight is now 128; at the time of beginning the treatment it was 106. Her work renders her susceptible to frequent attacks of acute nasal catarrh, but her lungs have remained free from involvement. This case illustrates what may be done even under adverse conditions, in the treatment of tuberculosis so long as it remains an unmixed infection.

Case XXIII.—Mrs. C. continues in good health, weighing 135 pounds. She has had no treatment and no cough since the summer of 1894. She is the wife of a poor farmer and the mother of ten children. This is another illustration of the good that may be accomplished by treating the disease in its earliest stages.

Case XXIV.—E. H. went to Colorado in November, 1894, and I am told that he continues well there. I have no more definite information concerning him.

Summary of the Cases Reported in 1894.—In my article of two years ago I reported twenty-four cases of tuberculosis treated with yeast nucleinic acid. Many of these were in the last stages of the disease when the treatment was begun. For details I must refer readers to the article. At the time of the report twelve (fifty per cent.) had died. Of the twelve then living, two have since died of tuberculosis

(Cases V. and XVIII.). Of the others, three (Cases II., XVII., and XX.) are certainly still infected with the disease. Of the seven others, I have recent knowledge of five (Cases IV., VI., XIX., XXII., XXIII.), and these now show no evidence of the disease. So far as I know, two others (XXI. and XXIV.), remain well. This gives 20.8 per cent. known to be free from the germs for the past two years, and 29.1 per cent. counting the two who were free from the germs when last examined. It will be seen that these percentages are figured on the twenty-four cases, many of which were in a hopeless condition when first seen.

Case XXV.—Miss E., a student, has been under my observation since first coming to the University, in October, 1892. Her history is briefly as follows: Her father died at the age of sixty-seven, after suffering for some months from cystitis. (There is a possibility that the affection of the bladder may have been tubercular.) Her mother is living and well. Mother had one sister and one brother die of consumption. She has four brothers, all of whom are well with the exception of one who has some irregularity of the action of the heart, supposed to be due to the excessive use of tobacco. She has one sister, who is well. She knows of no special exposure to tubercular infection. During the first two winters of her residence in this place she suffered from frequent attacks of subacute bronchitis, coughed much and raised abundantly. In the spring of 1894 this cough was very persistent, and I several times examined the sputum, but with negative results. In June, 1894, she went to her home in Iowa, and apparently improved much. For some reason she delayed her return to the University in the fall, and was still in

Iowa when she was attacked as herewith described: About 4 A.M., October 16, 1894, she awoke in an extremely nervous condition, and soon began to suffer from a severe cutting pain in the region of the left kidney. This pain soon became paroxysmal and excruciating. A physician was summoned and administered one-fourth of a grain of morphin hypodermically. This was followed during the day with repeated doses of chloranodyn, the pain continuing, but partly subdued by the medicines. Vomiting, possibly due to the anodynes, occurred in the afternoon. During the night she had a high fever, and her side remained sufficiently sore to keep her in bed for six days, and indoors four days longer. When she began to walk, she noticed that for some days every unexpected jar caused pain over the left kidney. Four weeks later she had a second similar, but less severe attack. After this she started on her return to Ann Arbor, but was compelled to stop for four days on the way on account of the pain in her side. This pain now returned daily, and was sufficiently intense to lead to the use of morphin. On November 27, 1894, this lady came to me and, after hearing the history of the attacks, as stated above, I did not doubt the correctness of the diagnosis of the Iowa physician, who had pronounced it renal calculi. I examined the urine, and was much surprised to find in it numerous tubercles, some quite as large as peas, rolled up, as it were, in epithelial cells. These contained bacilli in great numbers, and guinea-pigs inoculated with them developed tuberculosis. The urine contained no pus, blood, or albumin. Evidently the paroxysmal pains had been caused by the passage of these tubercular masses down the ureter. Nuclein injections were begun immediately, and continued daily for six months, then two or three times per week for another six months. Since October, 1895, no treatment has been given. The

injections were made deep into the muscles directly over the affected kidney. The renal pain became gradually less pronounced, and the urine has been found to be constantly normal since June, 1895. The patient passed through the winter of 1895 and 1896 without any of the "bad colds" which had been so frequent and persistent during the winter of 1893 and 1894.

Case XXVI.—Mrs. W., of Marshall, Mich., came to me in October, 1894. She had several small cavities in the upper lobe of the right lung and there was only bronchial breathing over the corresponding lobe of the left lung. The larynx was involved and deglutition painful. Her weight was 116. An unfavorable prognosis was given and treatment was begun under protest. This patient has been most faithful and persistent in her endeavors to carry out the advice of her physician in every respect. With the exception of cocain in spray and lozenges for the throat, nothing but the nuclein has been employed. For one year the injection was given every day. At the expiration of that time, I insisted that the treatment should be discontinued for a time, but the patient felt that she was losing ground without it, and since then she has had injections nearly every day. She has kept a record of every treatment and has missed it only twenty days in two years. The weight has increased and during the past year has varied from 126 to 132 pounds. The condition of the larynx is much improved; deglutition is painless, and the urine normal. The cavities remain practically unchanged. I examined this lady November 12, 1896. The left lung reveals no abnormality. The breathing over the right apex and subclavicular area is bronchovesicular. I do not think that I am attributing too much to the action of the nuclein when I say that it has retarded the progress of the disease. Indeed, her condition is

much better than it was two years ago. The temperature for the first year of treatment seldom had a maximum for the day less than 101° F. The maximum from September 17 to September 28, 1896, was 99°; from September 28th to October 2d, 98.3°; from October 2d to October 9th, 98.4°. It has been taken four times a day every day for the two years. Dr. Foote of Marshall has been associated with me in the treatment of this and the following case. The patient now raises but little, but bacilli are present.

Case XXVII.—Mrs. T., of Marshall, Mich., was first seen in December, 1894. Two brothers and one sister died of consumption. Patient has always had enlarged cervical glands. She lived in the same house with her consumptive sister during the illness of the latter. Patient has coughed for fifteen years, but this cough has been more constant for past six months. At the time of examination she was raising freely. Bronchial breathing and moist râles were heard over both upper lobes, showing that the area of involvement was large; but there were no cavities and the bacilli were found only after most minute search and frequently samples of sputum in which no bacilli could be detected were examined. This patient continued the use of the nuclein to June, 1895, when she had gained some ten pounds in weight and coughed much less. In the fall of 1895 the cough returned and she went to Florida. Dr. Foote writes me that this patient continued to improve so long as medicine was administered, but that she returned from the South with the disease much advanced and that he now regards her condition as hopeless.

Case XXVIII.—Mrs. K., of Holland, Mich., aged forty-four, was first seen December 5, 1894. Father died at sixty-five with some obscure trouble not named by the physician in attendance. Mother

died at fifty-six of consumption. Brothers and sisters have been free from tuberculosis. One of her mother's sisters and one of her father's brothers died of consumption. Patient has been coughing and raising for past three years. Some three weeks ago she went to Dr. King of Grand Rapids, who examined sputum and found tubercle bacilli. There is bronchial breathing over both upper lobes. The apices are retracted and there are probably small cavities in left lung. The afternoon temperature for three successive days before beginning the treatment averaged 101.5° F. This patient remained with me only three weeks. Since then she has been under the care of Dr. Kremers of Holland and Dr. King of Grand Rapids.

Dr. King sends me the following notes of this case:

1895. January 24. Returned from Ann Arbor, where patient had been under the care of Dr. Vaughan, who had employed nuclein solution hypodermically. The examination of the chest was made with much the same result as upon first examination, with exception that *moist* gurgling râles could now be heard at the left apex and bronchial breathing at the internal borders of both scapulæ. Cough and expectoration very slight. Appetite and digestion poor. At twelve o'clock noon, pulse 100; temperature, 99° F.

Patient placed upon "phospho-albumen," ʒ ii t.i.d., and benzoate of guaiacol, gr. iii t.i.d. Evacuant mixture when necessary for bowels; 70 minims one per cent. nuclein solution hypodermically, daily.

October 21st. Patient has been steadily improving. The treatment has been continued, and in addition, inhalations of creosote, eucalyptus and menthol are employed daily. At five o'clock P. M., temperature normal; pulse 100.

October 26th. Nuclein solution increased to 100 minims daily.

November 5th. Intercurrent "cold." Patient not so well.

November 10th. Improvement. Patient returned to Holland and the injections continued daily by husband.

1896. March 7th. Patient has been steadily improving in general condition. The areas of dulness have not increased and the râles, dry and moist, are entirely absent. For the past two weeks the nuclein solution one per cent. has been increased to 200 minims daily with good effect.

May 6th. Examination discovers no material change since March. About one week ago slight bloody expectoration; none since, however.

June 28th. The five per cent. solution of nuclein substituted for the one per cent., in daily hypodermic injections of 30 to 50 minims.

July 31st. Patient caught cold from exposure; increase of cough and expectoration.

August 5th. The five per cent. solution has been used continuously since June 28th, with success, although patient has not been quite so well as before the middle of July.

October 9th. The five per cent. solution has been continued, at times increasing the dose to 100 minims, with steady improvement. The areas of dulness are unchanged. There has been no extension of consolidation, and the patient enjoys comparatively good health.

The result up to date is eminently satisfactory to both the patient and myself.

Case XXIX.—J. B., of LaPorte, Ind., came to me in October, 1894. There was no family history of tuberculosis, or known source of contagion. This patient, aged twenty, is under size and weight, his greatest weight having been 118; weight at time of

beginning treatment 113. He began to have continued sore throat and hacking cough three years ago, but had been coughing up phlegm only during last two months. There were crepitant râles over apex and subclavicular area on right side. There was a small cavity between second and third rib on right side. The right lung showed general dulness on percussion. The left lung showed no abnormality. The amount of sputum was not more than two ounces in twenty-four hours, but it was rich in tubercle bacilli. There were no night sweats, and the afternoon temperature seldom exceeded 100° F. This patient improved rapidly. By January 1, 1895, the cough had ceased, the temperature was constantly normal, and the weight had reached a few pounds above the maximum. From this time to first of March, 1895, injections were made two or three times weekly. In March, 1895, the only evidence of disease in the lung was some dulness and prolongation of expiratory sound on the right side. However, an interesting bit of the history of this case follows: As has been stated, the cough ceased by January 1, 1895. In August of the same year, the young man coughed up a few mouthfuls of sputum and sent this to me. It contained a few tubercle bacilli. The cough did not continue. From October 1, 1895, to January, 1896, this patient had from two to three injections per week. By June the cough had stopped, and he felt so well that he discontinued the treatment. From June, 1896, to August 1, of same year, this patient had from two to three injections per week, as a precautionary measure. Since August 1, he has had no treatment. He now (October, 1896,) weighs eight pounds more than ever before and has no cough. Examined his lungs carefully October 22, 1896. A very slight prolongation of the expiratory sound over the right apex is the only evidence of abnormality.

This case is of especial interest inasmuch as it demonstrates that apparent cures do not always mean the complete destruction of the bacilli in the body.

Case XXX.—C. F., of Ypsilanti, Mich., a boy of seventeen, had numerous small cavities in both upper lobes when I first saw him in November, 1894. The treatment was given until February 1, 1895, when the patient was sent to Colorado. The first month of treatment seemed beneficial, but after that the disease progressed. In Colorado he had influenza and came home after four months and soon died.

Case XXXI.—Miss A., aged twenty-six, of Saginaw, Mich., had bronchial breathing over both upper lobes. Consumption had been diagnosed two years before, and she had spent the preceding winter in the Adirondacks. She had treatment, beginning in November, 1894, and continued for six months. She gained in weight, and coughed and raised less. The bacilli continued in the sputum and the physical signs showed but little change. I have not seen her since she discontinued the treatment.

Case XXXII.—Mrs. D., a colored woman, aged forty-two, living in great poverty, came under treatment in November, 1894. It was difficult to get any satisfactory family history. "Father died of chronic inflammation of the lungs, and one brother who was sick for a long while, died of pneumonia." She had been with both her father and brother in their last illness. Her bad cold had begun about one year before. During this time she had lost in weight, from 140 to 119 pounds. She coughed and raised profusely, and the sputum was rich in bacilli and in elastic tissue. There was a cavity in the right upper lobe and bronchial breathing on both sides. Treatment was continued as long as the patient was able to come to the office, which was about two months. The disease rapidly progressed and there was no evidence of

any beneficial effect of the nuclein. Death occurred a few months later.

CASE XXXIII.—J. H., of Yale, Mich., aged thirty-four. His mother died of consumption at the age of fifty-six, three years ago. He was her principal attendant during her last illness. In January, 1894, he began to cough, and could not speak above a whisper. He had been coughing ever since, and had lost thirty pounds in weight, when I first saw him, which was in December, 1894. He had a large cavity in the right lung, bronchial breathing over the left lung, and tubercular laryngitis. He remained under treatment for three months. During the first six weeks he improved in flesh, gaining nearly fourteen pounds in weight. His throat was treated with a spray consisting of equal volumes of the one-per-cent. solution of nucleinic acid and a saturated solution of boric acid. The condition of the larynx was much improved and the voice regained. However, during the latter half of his stay here, the condition of his lungs grew worse, and after going home he rapidly failed. The improvement was only temporary and, as stated above, the disease progressed while the treatment was being continued.

CASE XXXIV.—Miss B., aged seventeen, came to me December 4, 1894. She had tuberculosis of the right elbow-joint, which had been inflamed and painful for three years. This had been called rheumatism. The joint was discharging at the time of the first examination, and tubercle bacilli were found in this discharge. There was prolonged expiration over both apices, but no cough and no expectoration. There was a purulent discharge from the umbilicus. The afternoon temperature ranged from 100° to 101° F. The one-per-cent. solution of nucleinic acid was injected into the tissue about the joint and the sore was dressed with iodoform gauze. The nuclein was also injected for a few weeks about the um-

bilicus. The patient at that time remained under treatment until the first of July, 1895. Within six weeks after beginning the treatment, the temperature became normal, and has so remained, with one exception to be mentioned. By the first of June, 1895, the joint had so far improved that the young woman could use the hand in playing on the piano, could feed herself with the right hand and could use the arm in dancing. The discharge had ceased, the wound healed, and further treatment was considered unnecessary. This favorable condition continued until February, 1896, when the joint received two bad blows. Once it was struck with considerable force on the tire of a carriage wheel, and the second time the patient fell on the ice striking on that elbow. March 24, 1896, she returned with a swollen joint and a temperature of 100° F. Dr. Nancrede made an incision, and with a curette removed some tubercular matter. The arm has been carried in an aluminum splint since that time, and the wound washed out daily with the one-per-cent. solution of nucleinic acid. The five-per-cent. solution has been administered by the mouth in teaspoonful doses three times a day. Her general health remains good, and there is no abnormality detectable in the lungs.

[March, 1897. The wound has healed and the general health of the patient is excellent.]

I may call attention in this connection to the favorable reports made by Hitchcock [1] on nuclein in a case of hip-joint disease.

Case XXXV.—S. M., aged twenty-seven, of Bedford, Mich., was sent to me February 22, 1895, by Dr. G. W. Lowry of Hastings. His wife died of consumption August 8, 1894, after an illness of one year. The husband took care of her during this sickness. About three weeks before her death he began to

[1] *American Lancet*, January, 1895.

have a sensation of great weariness and some elevation of temperature. At the time of the first examination, the only physical evidence of the disease was a marked retraction of the left apex and a prolongation of the expiratory sound over this region and the subjacent area. He coughed very rarely in the morning and then raised some sputum, in which a few bacilli were found. The loss in weight had been about ten pounds. The afternoon temperature ranged from 99° to 100° F. After four weeks of treatment the normal weight was regained, the cough ceased entirely and the patient has remained apparently in perfect health since.

Case XXXVI.—E. A. R., a farmer, aged fifty-four, from Covert, Mich., came to me in November, 1894. His mother died of consumption many years ago. He was not with her in this illness. His mother's sister also died of consumption. One of his own sisters had been an invalid for fifteen years from a fall, and coughed much before her death. Another sister had died some seven years before of quick consumption. He had occasionally visited these sisters during their illness. Five years ago he had a hemorrhage, "followed by pneumonia." In 1890 he had a severe hemorrhage. From the time of the first hemorrhage, in 1889, he had not been well and had steadily lost flesh. In 1893 he had another hemorrhage, and still another about one month before he came to me. He was coughing and raising freely. The sputum contained numerous bacilli and some elastic tissue. His greatest weight had been 175, and at the time of the examination it was 152 pounds. There were numerous small cavities in the upper lobes. This patient remained with me only four weeks, but continued the treatment with Dr. Carnes, of South Haven. Dr. Carnes wrote me under date of March 1, 1895, as follows: "Mr. R. has been under the nuclein treatment now for three

months, in addition to the one month spent with you. He now weighs four-and-a-half pounds more than he did at Christmas. His temperature is practically normal all the time, seldom reaching 99° F. However, he coughs much, a clear, ringing cough, without much expectoration. He never before had a three-months' rest, and this has probably contributed to his gain."

A second report from Dr. Carnes under date of November 22, 1895, states: "He coughs much, and says that he cannot endure hard work, but it is plain to see that he is in better flesh and far more vigorous than he was last spring. He has for several years vacillated in this way, so I can see but little difference between the last year and several preceding years."

Recently (October 24, 1896,) Dr. Carnes wrote that this patient, who has had no nuclein now for more than a year, is gradually, but slowly failing in health.

CASE XXXVII.—Miss K., aged thirty-one, of Marinette, Wis., came to me for treatment in January, 1895. There was no known tuberculosis in the family, nor was there any discoverable direct exposure to the contagion. The patient had always been rather frail, her greatest weight having been 120 pounds. However, she had never been ill, until three years before, when she developed a "chronic bronchitis," accompanied by constant cough and profuse expectoration. Sixteen months before coming to me she had gone to Oregon, where she spent a winter, during which she gained thirteen pounds in weight and felt much improved, but even before her return home she began to fail again. Her appetite was very poor and her tongue heavily coated. The sputum contained numerous bacilli and much elastic tissue. There was bronchial breathing over the whole area of both upper lobes. There were

numerous small cavities in the same region. The patient remained under my treatment until June, 1895, when she returned to her home, and the nuclein treatment was continued by Dr. Hicks of Menominee, Mich. The result of the treatment was the same in this case as it has been in all others of the same class. There was temporary improvement, with increase in weight, reaching and even passing the previous maximum, and then retrogression, notwithstanding the continued employment of the nuclein.

Case XXXVIII.—Mrs. Q., aged thirty-two, of Gaylord, Mich., was brought to me in January, 1895. I say that she was "brought" to the office, and this is literally true. She was in the last stages of consumption, and after an examination, in which I found numerous cavities in both lungs, I advised her husband to take her home as soon as possible. However, he thought that an immediate return would discourage her so greatly that he insisted on a trial of the remedy for nothing more than its mental effect. This case illustrates what hope and nuclein, probably as much should be attributed to the former as to the latter, may do in the way of temporary improvement. This lady insisted on having full doses every day, and they were given. When I state that she gained twenty-five pounds in five weeks I expect to tax the confidence of the reader in my statements to the utmost; but such was the case. Her afternoon temperature fell from an average of 102° F. to less than 100°, and while she had to be brought in her husband's arms from the carriage into the office when she first came, before she left the city she walked many blocks at a time without feeling great fatigue. At the end of five weeks she insisted that she was practically well, and desired to go home. Believing that the arrest of the progress of the disease was only temporary, I made no objection. She returned home,

soon lost what she had gained, and died in September, 1895. I desire it distinctly understood that I do not attribute this great temporary improvement wholly to nuclein. It was one of those phenomenal cases of temporary improvement in which the bacillus seems for a time to have lost its virulence, and the vitality of the patient seems to spring into increased vigor at a bound. The nuclein was not used after she left, but I know that even had its employment been continued the relapse would have come with equal certainty.

CASE XXXIX.—M. G., a student, aged twenty-four, came to me in February, 1895, on account of a slight pulmonary hemorrhage which he had at that time. He was coughing up blood. This was examined and found to contain tubercle bacilli. Treatment was begun immediately and continued for two months. On the first examination moist râles were heard over the apex and subclavicular area of the left lung. The afternoon temperature frequently reached 101° F. for two weeks. After this it gradually fell to the normal. The young man continued his studies until June, 1895, when a physical examination failed to reveal any abnormality. He spent the winter of '95 and '96 in Colorado as a precautionary measure, and there has been no evidence of any disease since the treatment was discontinued.

CASE XL.—W. S., a stone cutter from Bluffton, O., came in February, 1895. This case is almost a duplicate of the one just described and several others of a similar character will be mentioned later. A brother-in-law of this man had died of consumption in his house, after a long illness, some months before. S. had a hemorrhage and came to me still raising sputum containing some blood. Bacilli were found but were not abundant. There were râles in the apex and subjacent area of the left lung. There was the characteristic fever curve. After four weeks of

treatment the lung cleared up and the man has continued in apparently the most robust health.

Case XLI.—Miss C., of Allen, Mich., came under treatment in March, 1895. There is no need of detail in this case. The disease was in an advanced stage with cavities and an afternoon temperature often as high as 103° F. There was temporary improvement indicated by a fall in the temperature and a gain in weight. This was followed by retrogression and a gradual decline.

After her return home Miss C. was under the charge of Dr. Williams of Jonesville, Mich., who has kindly furnished the following:

"After her return home from Ann Arbor, some time in the early summer of 1895, I continued the nuclein treatment, at first by internal administration, with negative results, as demonstrated by rise of temperature from 99⅘° to 103° F. Pulse 130. Respiration 22 to 24. Increase of cough, profuse expectoration, and return of night sweats. I then sent for a large syringe and treated her hypodermically, with the result that temperature, pulse, and respirations, were reduced. Appetite in a measure returned. Cough and expectoration modified, and a seeming arrest of the progress of the disease. This condition continued for about four months, or until late fall. During this time I gave her daily treatments at first, then as better symptoms returned, she came for treatment every other day. I injected from 30 to 80 drops of a one per cent. solution, and without the slightest symptom of an abscess at any time.

"From the first of November, until her death—some three months—the history of her case is that of tuberculosis in the last stage of the dread disease.

"While 'nuclein' hypodermically did not entirely arrest the progress of the disease I am satisfied it prolonged her life several months."

Case XLII.—Miss O., aged twenty-six, a student,

came under observation in March, 1895. Her mother and a sister and a brother of her mother and a brother of her father died of consumption. The mother died five years ago, after a long illness, during which the daughter attended her. This patient has always been frail and anemic. Four years ago her physician told her that one lung was diseased, and three years ago she had a long-continued low fever, which was called typhomalarial. She has coughed for four years. The quantity of sputum raised was small, but I never saw another specimen so rich in bacilli as was this. There was a large cavity on the right side, and râles were heard over the whole of the upper lobe on this side, and from the apex to the base in the left lung. The weight at the time of beginning the treatment was 98 pounds. The patient remained under my treatment until October 7, 1895, having an injection of nuclein nearly every day during this time. In October I could not see that her condition was materially different from what it was in the preceding March. Her weight was 100 pounds, and the physical signs remained practically unchanged. I advised her to go to Colorado, and she did so in October, 1895, and placed herself under the care of Dr. Henry Sewall, of Denver. In February, 1896, Dr. Sewall sent me the following condensed record: "Miss O., aged twenty-seven, with poor development and very anemic. Some percussion dulness and fine râles throughout upper half of right lung, and similar sounds found through the left lung nearly to its base; rather dry, cavernous sounds under right clavicle; pallor of pharynx and larynx, and slight swelling of mucous membrane over and between arytenoids. She has received nuclein injections every second day, or oftener, for two-and-one-half months, and has gained four pounds. Her lungs are drier and the morbid signs are less extensive."

In September, 1896, Dr. Sewall reported the continued improvement of this patient.

Case XLIII.—Miss G., aged twenty-five, of Brighton, Mich., came under my care in March, 1895. Her father died of consumption in 1891, and this young woman, always frail, was a constant attendant in his last illness. The mother is living and well. The patient has one sister, who has been married and away from her father's home for several years. This sister is in good health. A brother, who also was with the father during his sickness, has recently been declining in weight and failing in health. As stated above, the patient had always been frail. Her maximum weight was 108 pounds, and she has always been anemic. In 1893, while at the fair in Chicago, she caught cold, and has been coughing and expectorating ever since. The greater part of the winter of 1894 and 1895 had been spent in the South, but the disease had apparently made rapid progress during this time. At the time of her coming to me she was having "chilly sensations, followed by flushed cheeks, every day." There were small cavities in the right upper lobe, and bronchial breathing over the upper half of the left lung. She continued with me until October, 1895; and her history differs materially and favorably from the others of the same class. Up to the middle of August there seemed to be no improvement, and the afternoon temperature frequently went up to 103° F. At the time mentioned, the maximum daily temperature began to fall, the appetite improved and the weight increased. The physical signs showed marked improvement. During the latter half of September the temperature seldom exceeded 99° F. I thought this a good time to send the patient to Colorado. She went in October, aud has slowly improved without further medication.

Case XLIV.—Mrs. E., aged thirty-one, of Ann Arbor, came to me in April, 1895. One sister had con-

sumption for some years, but died in labor. This sister lived with Mrs. E., and as no precautionary measures were taken, the chance of transmission of the contagion was great. A brother, also, developed the disease, and his case will be mentioned later. For nearly a year Mrs. E. had been losing flesh and complaining of great lassitude. A pulmonary hemorrhage sent her to me. For five or six days she coughed up blood, and this was repeatedly examined. Tubercle bacilli were present, but were not numerous. The source of the hemorrhage was evidently in the left apex. Over the whole of the upper left lobe there was dulness, and moist râles could be heard. The afternoon maximum temperature was for some days as high as 102° F. Treatment was begun immediately, and continued daily until October, 1895. From this time to March, 1896, the injections were made twice a week. Since March the patient has had no treatment. She weighs now 25 pounds more than her maximum weight before April, 1895. I can now (October, 1896) find no trouble in the lungs.

Case XLV.—Mrs. S., aged twenty-six, of Chester, Mich., came under my observation in April, 1895. There was a history of direct contagion. She had helped to care for a consumptive neighbor and no precautions against infection had been taken. The patient was in an advanced stage of the disease. There were numerous small cavities on the left side and consolidation on the right in the upper lobes. The maximum temperature was from 102° to 103° F. The treatment was administered for three weeks without any appreciable effect on the rapid progress of the disease. Death occurred within a few weeks after the patient's return home. In this case there was not even a temporary improvement.

Case XLVI.—V. F., aged twenty-four, a medical student, had a hemorrhage in April, 1895. Tuber-

cle bacilli were abundantly present in the blood. There was the pneumonic infiltration and the characteristic fever of tuberculosis. Treatment was given daily to October, 1895, then omitted to February 25, 1896, then three time per week until June, 1896. The summer of 1896 was spent in the Adirondacks without treatment. During this time the disease progressed. When he left Ann Arbor in June, 1896, he had no cough. On his return he was raising some sputum every morning and this contained bacilli. October, 1896, he has returned to college and I find bronchial breathing over the right apex. He now weighs 145 pounds, more than he ever weighed before, but, as stated above the sputum contains bacilli.

Case XLVII.—G., aged twenty-one, of Ann Arbor, is the first of a class which has furnished me with only a few representatives. There was no hemorrhage, but the patient was brought to me on account of a "bad cold" and a cough which had persisted for "some days." The maximum daily temperature was between 101° and 102° F. going occasionally, but exceptionally, to 103° F. There was bronchial breathing with moist râles over the upper half of the left lung. The sputum contained numerous tubercle bacilli. Treatment was continued until October, 1895. The bacilli disappeared in August, and the cough ceased a little later. The temperature became constantly normal about the time the bacilli disappeared. The râles and the dulness disappeared, and the only suspicious sound heard on auscultation was due to some prolongation of the expiratory act. Late in the fall of 1895 this patient went to Colorado as a precautionary measure. He remains there and reports himself well. I believe that in this case the tubercular invasion had not extended very far when the treatment was begun.

Case XLVIII.—Mrs. D., aged thirty, of Ann Ar-

bor, belongs to the same class as the preceding one. She had a cough in February, 1895, when I examined her lungs, and believed from the evidence thus obtained that she had tuberculosis, but repeated examinations of the sputum which she was then raising quite freely failed to reveal any tubercle bacilli and the nuclein was not used. After continuing for two weeks the cough ceased. In April another bad cold with cough and expectoration brought her to me again. This time the bacilli were found. Treatment was given for three months and then wholly discontinued. The cough ceased in a few weeks as it had done before, and she passed through the winter of 1895 and 1896 without a "bad cold." She was pregnant at the time of treatment and has borne a healthy child since. Now, there is no evidence of the existence of tuberculosis.

CASE XLIX.—K., a medical student, aged twenty-five, spent the summer of 1894 partly in taking care of several tuberculous patients. In May, 1895, he had a hemorrhage. In the bloody sputum the tubercle bacillus was easily found. The nuclein treatment was begun immediately and continued for two months. He then went to Colorado and located at Fort Collins where he practices medicine. He reports himself as being quite well.

CASE L.—Mrs. L., of Jackson, Mich., aged thirty-two, came to me in June, 1895. She had three children, all of whom were well. The father was then living and well. Her mother died at the age of forty-one of consumption. Four of her mother's and one of her own sisters died of consumption. She had been with this sister during her illness. The patient began to recognize the fact that she was not well early in the fall of 1894. She began to cough and raise about January 1, 1895. At the time of the first examination she was coughing and raising very profusely. She had exhausting night sweats. The

average afternoon temperature for four days before the first injection of nuclein was 102° F. There was bronchial breathing over both upper lobes. The appetite was poor. This patient improved temporarily, then lost what she had gained. The treatment was continued about three months, and the condition at the close of this period showed no improvement. She died in August, 1896.

Case LI.—Mrs. W., aged thirty-eight, of Lima, O., was first seen early in June, 1895. She had been married fifteen years, and had two healthy children. Her father had died at the age of seventy-six and her mother was then living at the age of eighty. She had seven sisters, one of whom had died about two years before of consumption. She had been with this sister during her illness. She had her first hemorrhage in May, 1894, and had coughed and raised some ever since. Strange to say that during this year she had gained in flesh. She was in good flesh (I find that I failed to record her weight), and did not by any means present the appearance ordinarily supposed to be characteristic of consumption. There was bronchial breathing over the whole of the left upper lobe and over the greater part of the right upper lobe. The amount of sputum raised was small, but it contained the bacilli in great numbers. Her appetite was good, and she retained her healthy appearance as long as she was with me, which was until the middle of October, 1895. This patient did not do well. Hemorrhage followed hemorrhage. The quantity of blood raised at a time was small, but it was continuous. I cannot say that there was even temporary improvement. The temperature seldom went as high as 100° F. In October, 1895, she went to Denver, where she continues to reside. The hemorrhages still occur.

Case LII.—Miss R., aged twenty-eight, was sent to me by Dr. Steiner of Lima, O., in June, 1895.

Father and mother were living and well. One brother died of consumption six years ago. The patient was with this brother during his illness. She had been teaching for eleven years in the public schools of Lima. She had influenza four years ago, and has been more or less hoarse, with some cough, since that time, but she has attributed this condition to the unwholesome air of the schoolroom and to the constant use of her voice. During the vacation of 1894 she worked in the slums of Chicago, although at that time she was feeling much out of health. She first consulted a physician in May, 1895, when she went to Dr. Steiner, who immediately recognized the true nature of her trouble. Respiration over both upper lobes was wholly bronchial. The sputum was purulent and contained numerous bacilli. The maximum temperature averaged 100° F. She rapidly improved temporarily until the middle of August, when she had a chill every other day for a week, her tongue was heavily coated, and she loathed food. A mercurial, followed by large doses of quinin, seemed to remove this trouble, which I regarded as an intercurrent attack of malaria. She soon began to improve, and I consented to her returning to Lima and resuming her work as a teacher. Some three weeks later she suddenly developed a pleuritic effusion on the left side. Some of the fluid was drawn by Dr. Goebel and sent to me. It contained tubercle bacilli. Notwithstanding the most intelligent treatment by Dr. Goebel, the patient rapidly failed, and died in February, 1896.

Case LIII.—Mr. G., aged thirty-two, of Detroit, was examined July 5, 1895. There was no family history of tuberculosis. Both parents were then living, and his two brothers were healthy, active business men. The patient has been for some years given to the abuse of alcoholic drinks. Within the preceding twelve months his weight has fallen from

170 to 120 pounds. Examination showed extensive involvement of the lungs and larynx. Both apices were retracted. There was a large cavity on the left side under the third interspace. Crepitant râles were heard over the upper half of the right lung. Moist râles were heard posteriorly both above and between the scapulæ. The expectoration was abundant, purulent, and full of bacilli. Considering the condition of his lungs, this is in some respects one of the most satisfactory cases which has come under my treatment. During the first two months I could not see the slightest evidence of improvement. Indeed, the disease steadily progressed. The afternoon temperature frequently went as high as 103° F, and the weight slowly diminished, but early in September, 1895, the appetite improved, the cough became much less continuous, the sputum lost its purulent character, and in several samples no bacilli could be found. This would be true sometimes when all the sputum raised in twenty-four hours was collected and examined. At other times a few bacilli could be found. This condition of the sputum continued as long as the patient was with me, which was until December 21, 1895. There was also marked improvement in the physical signs. The cavity remained, and there was bronchial breathing over both upper lobes, but there were no râles. Dr. McClintock has examined this patient (October, 1896), and reports that there has been further improvement, and that he is now using the nuclein again.

Case LIV. — Miss B., aged twenty-seven, of Owosso, Mich., a stenographer, was examined July 9, 1895. Her father died at forty-five from some stomach trouble. Her mother is living, and apparently well, but earlier in life she had pulmonary hemorrhages. A sister of her mother and a brother and sister of her father died of consumption. Miss

B. has been "out of health" for three or four years, but did not begin to cough until four months ago, when she had an attack of influenza. Since then she has been coughing and raising abundantly. She had heavy night sweats, and the menses have been suppressed for some months. There was at least one cavity in the left lung, and there was bronchial breathing over the upper lobe on the right side. The patient remained under treatment with me until about October 1, 1895, when she went to Talapoosa, Ga., where the nuclein injections were continued by a very intelligent physician. The result in this case conforms to the general rule for this class. There was temporary improvement, gain in weight of about ten pounds, restoration of the menses, diminished cough and expectoration, and then under the continued use of the nuclein, retrogression and gradual failure. She died in August, 1896.

Case LV. — A. B., aged twenty-one, farmer, Hersey, Mich. One brother and one sister had died of consumption within the past five years. Patient was with both brother and sister during their illness. He had lost about twenty pounds during the last year. Right lung: Bronchial breathing throughout upper lobe; crepitant râles in the superior axillary region. Posteriorly a large cavity was detected above the scapula. There was bronchial respiration between the scapulæ. Left lung: Bronchial respiration over upper lobe; crepitant râles through the lower part of the lung and throughout the axillary area. Bubbling râles were heard posteriorly.

There was an ischiorectal abscess, which had been opened by his physician in March, 1895, and which at the time of my examination was discharging freely. This abscess was opened more freely and dressed with nuclein and iodoform, and healed completely within one month. This patient remained under treatment until October 1, 1895. His lungs showed some im-

provement in physical signs, and the weight increased four pounds. The temperature was not materially altered, that for 4 P.M. averaging 100° F. during the first and last weeks of treatment. When he went home, October 1, 1895, I gave him a prescription for capsules, containing one grain each of iodoform and sulfate of quinin and one-sixtieth of a grain of strychnin sulfate. I have been unable to obtain further information concerning this patient.

CASE LVI.—Miss W., aged twenty-five, of Ann Arbor, was examined July 10, 1895. Her mother died five years ago of consumption. Miss W. was with her mother during the illness of the latter. Her mother had two sisters, both of whom died of consumption. Miss W. had not felt well since the death of her mother. She had lost ten pounds since June 1, 1895. She had been having night sweats for two months, and felt "flushed and hot" every afternoon. The cough was slight, and the sputum consisted of glairy mucus, containing a few tubercle bacilli. The only abnormality which could be found in the lungs consisted of crepitant râles in the right apex. The afternoon temperature ran from 99.5° to 100° F. The râles disappeared, and no germs could be found after three weeks of treatment. The injections were continued until October 1, 1895. The patient has shown no signs of disease since, and raises nothing.

CASE LVII.—Mr. R., aged thirty-two, of Toledo, O., was examined July 10, 1895. He had no family history of tuberculosis, but there was sufficient evidence of direct exposure to the infection. A young man with tuberculosis had worked for many months in his office. This clerk had coughed and expectorated freely, and there had been no attempt to disinfect the sputum, and it was R.'s recollection that the clerk had expectorated on the floor. This was some five years before he came to me. He had known himself to be tuberculous for about two

years, and had spent a part of one winter at Asheville, N. C. There were numerous small cavities in both upper lobes. The afternoon temperature went as high as 101° F. The treatment was continued until the middle of September, 1895, when he went to Utah for permanent residence. I have not heard from him since. There was a slight gain in weight during treatment, but no essential improvement in physical signs.

CASE LVIII.—Charles M., aged seventeen, of Northfield, Mich., was examined August 13, 1895. There was no history of tuberculosis in the family, and no evidence of direct contagion. In March, 1895, he began to cough, and from that time to the date of examination he had lost fifteen pounds in weight. The amount of sputum raised daily averaged about two ounces. There were a few bacilli. Moist râles could be detected in the right subclavicular area. No other abnormality could be found. The average temperature for three days before beginning the treatment was at 8 A.M. 99°; at 12 M., 99.4°; at 4 P.M., 100°; and at 8 P.M., 98.6°. The treatment was continued until the middle of September, 1895. By this time the temperature had become constantly normal. The cough and expectoration had ceased, and he had gained ten pounds. He remains well, and has no cough.

CASE LIX.—Miss L., aged twenty-eight, of Detroit, was first examined August 13, 1895. One sister had died of consumption at the age of twenty, eight years ago. Miss L. had been with this sister during her illness. She had been coughing for three years, and was in the last stages of the disease. There were numerous small cavities in both upper lobes. The afternoon temperature went as high as 102.5° F. The treatment was continued for eight weeks, and without effect on the progress of the disease. She died about three months later.

CASE LX.—Mr. C., aged thirty-seven, of Amsterdam, N. Y., a druggist. There was no family history of tuberculosis and no evidence of direct contagion. Patient had influenza six years ago, and has been coughing and expectorating ever since. There were cavities in both upper lobes. Treatment was given for two months without benefit. He died the last of December, 1895. During the last week of his life there was involvement of the meninges.

CASE LXI.—Mrs. C. of Amsterdam, N. Y., wife of the patient whose history has just been given. There was no family history of tuberculosis, but she undoubtedly acquired the disease from her husband. It may be remarked here that Mr. C. was exceedingly careless about expectorating about him wherever he happened to be. This was so noticeable and he was so persistent in the neglect of my admonitions so frequently given, that I once forbade his coming to my office. This caused him to heed my advice while in my office, but he continued to disregard all precautions elsewhere. Mrs. C. also had numerous small cavities. The treatment was given for about two months, but without any evidence of improvement. She died a few weeks after her husband.

CASE LXII.—E. B., aged twenty-eight, of Saginaw, Mich., was examined August 14, 1895. The family history has already been given. One sister died, while tuberculous, in child-birth, and another sister was under treatment (Mrs. E., Case LXIV). This man had always considered himself especially healthy and robust. About six weeks before coming to me, he began coughing and spitting up blood. He had had three slight hemorrhages in that time, and had lost twelve pounds in weight. The only abnormality that could be detected consisted of a prolonged expiratory movement over the left apex and subclavicular area. The sputum contained numerous bacilli. He remained with me only three weeks and

went home with the intention of having the treatment continued. October 23, 1895, he wrote me that he had gained eight pounds. He sent me some of the sputum at that time, and there were bacilli in it. November, 1896, he reports to me that he is quite well, weighing more than he ever did before, but I have not seen him.

Case LXIII.—Mrs. H., aged thirty-eight, of Toledo, Ohio, came for treatment August 18, 1895. She had been coughing and expectorating for two years, and had spent one winter at Colorado Springs. The expectoration was free, but contained very few bacilli. There was only bronchial breathing over the upper half of the left lung and over the right apex. She remained under treatment for two months, during the latter half of which she coughed and expectorated much less and no bacilli could be found, although frequent and careful examinations were made. I last examined the sputum in December, 1895, and at that time could find no bacilli.

Case LXIV.—Miss P., aged eighteen, of Grass Lake, Mich., had been seen by me in consultation early in July, 1895. She was in the last stages of the disease, very much emaciated, and with extensive cavities. There was no family history of the disease, except that a cousin had it, and this cousin had visited at her father's house. The treatment in this case was without effect, and the patient died in November, 1895.

Case LXV.—Miss M. S., aged twenty-one, of Ann Arbor, in the last stage of the disease had the treatment for three weeks without effect.

Case LXVI.—Miss E. S., aged twenty-nine, of Ann Arbor, came for examination August 29, 1895. There was no family history and no known direct contagion. The apex and subclavicular area of the left side showed crepitant râles. The sputum was small in amount but contained numerous bacilli.

Miss S. is a farmer's daughter and lives about five miles from my office. She drove this distance every day, rain or shine, cold or hot, from the time of beginning the treatment until March 1, 1896. I attribute much of the good results secured in this case to that drive. The germs disappeared in December, 1895, and she has not coughed any since early in January, 1896. Physical examination fails to show any abnormality. The temperature never went above 100° F. and has been normal since December, 1895. I believe in the curative value of out-door life. This adjunct to treatment is especially applicable to those cases in which there is but little elevation of temperature.

Case LXVII.—Mr. W., aged twenty-eight, a paperhanger, of Ann Arbor, came for examination the last of August, 1895. There was no history of the disease in his family, and no evidence of direct contagion. He came on account of a hemorrhage, having supposed himself well except that he had lost about fifteen pounds in weight during the preceding year. The bloody sputum contained numerous tubercle bacilli. The left lung showed in its upper portion moist râles. The afternoon temperature was 100° F. After four weeks of treatment the râles disappeared and there has been no cough since. He took the injections daily for nearly six months. He now weighs more than he ever did before, and has not lost more than one month from his work during the whole time.

Case LXVIII.—Mrs. W., aged twenty-eight, of Grand Rapids, Mich., was examined early in September, 1895. There was no history of the disease in her family, and none of direct contagion. There was bronchial breathing over both upper lobes. Treatment was given for six weeks, during which time the patient gained a few pounds in weight and the night sweats, which had been profuse, ceased.

She then went to Colorado, and I have known nothing of her since.

Case LXIX.—Miss R., of Goshen, Ind., was examined late in September, 1895. She had numerous small cavities, profuse night-sweats, and high afternoon temperature. The treatment did not retard the progress of the disease.

Case LXX.—Mr. J., aged twenty-seven, an instructor in the University, came under treatment early in October, 1895. There was no history of the disease in his family. He had worked in the same room with a consumptive two years before. There was bronchial breathing over the upper half of both lungs. The afternoon temperature averaged 100° F. The treatment was continued until the middle of February, 1896, at which time he went west for permanent residence. There was some improvement during the treatment, as shown by gain in weight and decrease in temperature. However, the bacilli remained in the sputum and the physical signs were not materially altered. November, 1896. He has steadily declined in health since going to Colorado.

Case LXXI.—Miss S., aged eighteen, of Bay City, Mich., October 13, 1895. There are certain points in this case which justify some detail. Miss S. had studied very continuously in the Bay City High School, the very moderate means of her parents having rendered it necessary that her studies should be pursued under certain disadvantages. During the last year of her high school course she lost flesh and suffered from a sensation of general weariness from which she constantly strove to relieve herself by working all the harder, and the stimulation of work actually gave her temporary relief. In October, 1895, she entered the University and soon thereafter consulted me concerning the feeling of lassitude. Nothing had called her attention to her lungs. She had observed that she felt a shortness of breath, even when

walking at an ordinary gait, and much more plainly on ascending stairs, but she had supposed that this was due to a weak heart.

There was bronchial breathing over both upper lobes and both apices were retracted. There had never been any cough. The extent of lung involvement was certainly unusually great considering the entire absence of cough. The physical examination left no possible doubt in my mind as to the nature of the trouble and subsequent developments confirmed the testimony of the physical signs. The patient was put on creosote, and the administration of nuclein was not begun until later. In November, she had a slight hemorrhage and the blood raised at the time was carefully examined, but with negative results. The cough accompanying the hemorrhage soon ceased. I had requested the patient to keep a wide-mouthed bottle in her room and to bring me anything and everything she should cough up. Several times she brought me samples of saliva and mucus from the throat and nares. Early in January, 1896, I found the bacilli for the first time; then the nuclein was given. However, the lungs rapidly broke down. She was carried to Colorado in February and died there about three weeks later. This case illustrates in an unusual manner how extensively the lungs may be involved in tubercular processes before the bacillus appears in the sputum, and indeed before there is any sputum.

Case LXXII.—Mr. M., of Grass Lake, Mich., principal of the high school, was examined November 21, 1895. He had considered himself well until about three weeks before this examination, when he began to cough and raise. There was no physical sign except prolonged expiration accompanied by feeble moist râles over the left apex and subjacent area. The sputum was small in amount, but contained numerous bacilli. He remained under treat-

ment for about four weeks, when on having an opportunity to accept a position in New Mexico, he went there. He improved slightly in weight during the treatment. There was no family history of tuberculosis; but he and his wife had during the summer of 1895 occupied the house of Mr. P., father of Case LXIII. Of course he might have been infected much earlier than this. However, I think this coincidence of sufficient importance to be recorded.

Case LXXIII.—C. M., aged twenty-five, of Pinkonning, Mich., a fireman on a locomotive. There was no family history of tuberculosis and no known direct exposure to contagion. In December, 1893, he fell on a switch-stand, bruising the abdomen and injuring one testicle, which has gradually decreased in size until it is not more than one-third as large as the other one. The injury to the abdomen caused a dull pain, which continued for some months. This pain grew so severe in February, 1894, that he summoned a physician and was in bed for one week. The physician said that he had inflammation of the bowels. Some six months later he began to cough. He had been under the charge of a physician for three months before coming to me. He had suffered during this time from a persistent diarrhea. Had profuse night-sweats, and was raising abundantly. It seemed to me that the disease had extended from the abdominal cavity upward. Both lower lobes were involved and there was a pleuritic effusion on the left lung. The afternoon temperature went as high as 103° F. This man had the nuclein injections for three weeks, during which time there was some improvement in the diarrhea, but none in the lungs. He was anxious to go west, the railroad company offered him transportation, and as I did not believe that his condition would be materially benefited by the nuclein treatment, I consented. He went to Arizona and I have heard noth-

ing further from him. I should be much surprised if the change in climate has done him good.

Case LXXIV.—C. T., aged twenty-three, a student from Lansing, Mich. His father's half-brother had died of consumption eight months before, after a long illness in his father's house. T. had always been frail. He began to cough and raise some one year ago. Since October 1, 1895, the amount of sputum had greatly increased. His hands and feet grow cold every afternoon. There was roughened breathing over the whole of left upper lobe and some dulness over the right side. The first examination failed to reveal any bacilli, but subsequently a few were found. The injections were given for four weeks, when the cough ceased, the fever disappeared, and six pounds in weight was gained. The only evidence of any trouble in the lungs on his discontinuance of the treatment was a prolonged expiratory murmur on the left side. November, 1896, he writes that he is perfectly well.

Case LXXV.—Mrs. C., aged twenty-nine, of Seattle, Wash. There was no family history of the disease and no known exposure. She had left Seattle in September, 1895, and gone to her father's at Towanda, Pa., where she had been under the treatment of Dr. C. M. Pratt, who wrote me as follows: "Mrs. C. has been under my care for the past month for symptoms of incipient phthisis, cough, rapid pulse, night-sweats, delayed menstruation, etc. She is now somewhat better, weight increased, cough less, night-sweats better, and she has menstruated. Her treatment has been creosote, phosphate of iron, and one-sixtieth of a grain of picrotoxin for night-sweats." I found bronchial breathing over the upper part of the left lung. The quantity of sputum was small and bacilli few. Her weight was 116 pounds. She had the nuclein injections for nearly three months, before which

time her cough had ceased altogether and no abnormality could be detected in the lungs. Under date of August 16, 1896, she wrote me from Sidney, Wash., that she weighed 133 pounds and had never felt so strong and well. She has not been troubled with colds and has no cough.

CASE LXXVI.—Mr. H., aged twenty-four, of Decatur, Ill., came to me in August, 1895. It will be seen that this case is reported out of chronological order. This is done because it was not a case of pulmonary tuberculosis. The disease was located in the bladder. He had been troubled about three months before consulting me with frequent and painful micturition. He had been sounded for stone with negative results. Examination of the bloody urine showed the presence of numerous pin-head lumps, which, on being crushed between cover glasses and stained, revealed great numbers of tubercle bacilli. Guinea-pigs inoculated with the urinary sediment developed tuberculosis. The treatment was begun by me and continued by Dr. Barnes of Decatur. Early in September, 1895, he began his work as teacher in the Decatur High School. At that time his afternoon temperature frequently rose as high as 103° F. Before December, 1895, the urine had become normal, and had so remained. There is now no evidence of the existence of any disease.

Summary.—The cases reported in this and the preceding paper include all those in which the tubercle bacillus was found, treated by me with yeast nucleinic acid, from May, 1893, to December, 1895. There has been no selection of cases to report, and no exclusion. Many were in the last stages of the disease when the treatment was begun. Indeed, some of them were at that time confined to their rooms, and died within a few weeks. In my

study of the value of yeast nucleinic acid in the treatment of tuberculosis, I have endeavored to carry out the investigation as I would a series of laboratory experiments and, above all, not to deceive myself. Of the seventy-six cases reported, seventy are those of pulmonary tuberculosis. Of these, thirty (42$\frac{6}{7}$ per cent.) have died. Of these, at least nine were temporarily benefited.

Of the seventy, seventeen (24$\frac{3}{7}$ per cent.) have been continuously free from the bacillus for from one month to two and one-half years, so far as can be determined from the sputum; *i.e.*, either there has been during this time no sputum to examine or that examined has failed to reveal the bacillus. To the best of my knowledge, another (No. 47) has been free from the bacillus for more than a year, and another (No. 29) has been free from the bacillus with the exception of a short time, and still another (No. 24) was free when last examined. Twenty (28$\frac{4}{7}$ per cent.) were still infected at the last examination. Of these, sixteen have been apparently improved by the treatment. It should be stated that none of these were hospital cases. I was not able to control their diet. Most of them were not rich, and had only inexpensive food. The hygienic conditions under which many of them have lived have not been satisfactory.

Of the five cases of urinary tuberculosis, four have apparently been cured. One was temporarily benefited, but developed acute miliary tuberculosis and died. The one case of joint tuberculosis has been benefited.

Since the first of January, 1896, I have treated be-

tween thirty and forty additional cases of pulmonary tuberculosis with nuclein, but since most of these have been given the five and the ten-per-cent. solutions of nucleinic acid by the mouth, some with and some without hypodermic injections of the one-per-cent. solution, and since sufficient time has not elapsed to draw positive conclusions concerning the value of this method of administration, I will defer further details until another time. Moreover, to report additional cases would require that this paper be lengthened beyond all proper limits.

I have treated several cases which I believed to be tuberculous, but the bacilli could not be found. These are not included in the list already given, and I will now proceed to detail two which seem to me of special interest:

In May, 1895, I was called to Battle Creek, Mich., where I saw, in consultation with Dr. Alvord, a Mr. D. His mother's family had furnished several consumptives, and a brother had had one leg amputated by Dr. John B. Hamilton of Chicago on account of tuberculosis of the knee-joint. The patient, who was unmarried and twenty-eight years old, had been failing in health for the past six months, latterly very rapidly. February 1, 1895, he weighed 136 pounds; at the time of my visit eighty-two pounds. He had an exhaustive mucus diarrhea, with night-sweats, and the temperature curve of tuberculosis. The lungs were normal and the heart very weak, but without organic disease. The abdomen was retracted, and no enlarged glands could be found. A few weeks before my visit Dr. Alvord had operated upon him for fistula in ano. The wound was still discharging. I examined the stools and the pus from the wound for tubercle bacilli, but with a negative result. I ad-

vised that the bowels be irrigated two or three times a day with large volumes of water, and that after each irrigation two drams of the one-per-cent. solution of yeast nucleinic acid with fifteen drops of laudanum be injected. Teaspoonful doses of the nucleinic-acid solution were also given by the mouth three times a day. From the time of my visit until September 1, 1895, about one gallon of the nuclein solution was used, and the patient gradually improved. By September, 1895, he was able to walk out, and in January, 1896, he resumed his work. He has continued well. His present (November, 1896,) weight is 130 pounds. He eats without discrimination, has daily normal movements, and attends to his duties as proprietor of a dry-goods house.

Miss S., of Port Huron, Mich., aged eighteen, came to me by the advice of Dr. Wilson of that place, April 4, 1895. Father and mother are both living and well. In short, the only consumptive in the family is a cousin, with whom the young lady has occasionally visited. Her weight had fallen from 129 pounds to 105 pounds within six weeks. Night-sweats were profuse and exhausting. The following letter from Dr. Wilson forms the best statement of the history of the case:

Port Huron, April 9, 1895.

DEAR DOCTOR:—I had intended to send with the patient a statement of the origin and progress of the lung involvement, but I misunderstood the time fixed for the departure and was too late.

I think it was February 18th, that her mother brought Miss S. to me. She was very anemic, weak, and feverish. I made no examination of the lungs at that time, but did four days later. I was again struck with the great anemia. The exertion of walking across the room would cause very rapid pulse and breathlessness. I found the upper part of the left lung involved. About two weeks after this, Dr. Stewart, on my invitation, examined the lung, and found a small area of dulness about the line

of junction of the upper and middle lobes of the right lung. On examination I confirmed this discovery. The dulness spread up and down and in all directions from this focus, and within two weeks involved the whole of the right lung. I watched its progress closely, and know this to be a fact. The afternoon temperature soon reached 100° F., then ran up to 102°, to 103°, and sometimes to 104° F. At times I doubted my diagnosis of tubercular infection, as the cause of the dulness, but could find no other solution for it. At the time she left, the dulness was not quite so marked in the right apex as it had been. There was very little cough, for the amount of lung involved, and she had certainly gained in strength, but had lost in weight. Her appetite had also improved, and there was a morning remission in the fever, which before had been continuous. I had the nuclein and thought of using it, but concluded that it promised nothing in a case of such acute nature, so I prescribed tonics and remedies to meet symptoms as far as possible. I will be glad to hear from you concerning her. Yours,

MORTIMER WILSON.

Menstruation had not appeared for three months past. The mother told me at the time of examination that the patient had been failing in health noticeably since early in December, 1894. My notes taken at the examination read: "Upper lobe of right lung partially consolidated and numerous râles heard throughout upper lobe of left lung. There is a distressing cough, but the patient has never raised anything." The temperature the day before beginning the treatment was as follows: 8 A.M., 98.5°; 1 P.M., 101°; 4 P.M., 103°; 8 P.M., 102⅜° F.

The treatment was begun April 5th with 40 minims, which was doubled the next day, and kept at 80 minims during the course of the treatment. The temperature gradually fell as is shown by the following: May 8, 8 A.M., 98.5°; 12 M., 100⅘°; 4 P.M., 101¼°; 8 P.M., 100⅜° F. By the middle of June the temperature remained normal, and there has been

no fever since that time. When I state that the temperature gradually declined I would not have it understood that there were no exceptional days. In the latter part of April the temperature for some days ran high at 4 P.M., and once reached 104° F. The treatment was discontinued the last of June, and there has been no occasion to resume it since. At that time the lungs were quite normal and the cough and night-sweats had ceased. In October, 1895, Miss S. wrote me that she weighed 130 pounds and was quite well. In March, 1896, I saw her and she was apparently in the best of health. I did not examine her lungs.

I have reached certain positive and definite conclusions concerning the value of the one-per-cent. solution of yeast nucleinic acid in tuberculosis administered daily in doses of from 60 to 80 minims hypodermically, and these conclusions I will now give:

1. In advanced stages of the disease, in which the area of involvement is great, with or without cavities, the best that can be expected from this treatment is temporary improvement. Even this does not occur in all cases.

2. In inital cases, when the area of infection is limited, this treatment may and often does, not only arrest the progress of the disease, but it acts as a curative agent.

If these conclusions be correct, it follows that in order to save our tuberculous patients by the employment of this treatment, we must recognize the disease in its incipiency. How can we best do this? That the presence of the bacillus tuberculosis in the sputum is a positive and conclusive proof of the ex-

istence of pulmonary tuberculosis, I assume that no one will deny. If the sputum were examined for the bacillus in every case in which there is any sputum, and as soon as there is any, thousands of cases of tuberculosis would be recognized in time for therapeutic measures to be effective. I employ the word "sputum" here as I think it is generally understood by the profession, and not as it is defined in our medical dictionaries, nor do I use it in strict accord with its etymology. I mean to designate by the word "sputum" any secretion which has its origin in the air passages below the epiglottis, and which is ejected from the mouth. It will be seen that according to this definition saliva is not sputum, though the latter may be mixed with the former. With this definition, I say that in any instance in which the patient raises any sputum, an examination for tubercle bacilli should be made. Neither the robust appearance of the patient nor his previous excellent health, nor his family history, possibly free from any taint of tuberculosis, should cause the physician to neglect this examination. As a profession, we have been so long, so forcibly, and so painfully impressed with the old, classical picture of this disease, when it was known only in its last stages, that even now we too often fail to recognize it in the distance from failure to employ the aids to our vision with which science has recently equipped us. It is my belief that, so far as tuberculosis is concerned, our profession is to-day in greater need of skill among its members in the early recognition of the disease than it is of therapeutical agents with which to combat it.

While the careful examination of the sputum would be of great service in the early recognition of tuberculosis, I believe that in many cases the diagnosis of this disease may be and should be made before there is any sputum to examine. I will illustrate this point by the history of the following case, which I have just examined, and which might be duplicated almost any day in the practice of one giving special attention to this disease:

Miss G., aged twenty-six, a saleswoman in a dry-goods store. Her mother died, twenty years ago, of consumption. One sister died twelve years ago of the same disease. The family has lived during all this time in the same house. During the summer of 1894, Miss G. weighed 130 pounds, and was apparently a robust, vigorous woman. In August, 1895, she weighed 118 pounds, and consulted a physician for the first time in her life. She complained of great and constant weariness, loss of appetite and chilly sensations, followed by slight fever, every afternoon. The physician to whom she went in August, 1895, has treated her from that time until now for malaria and "liver trouble." In March, 1896, she had the *grippe*, and began to cough, for the first time in her life. She has been coughing ever since. Now she weighs 104 pounds, has profuse night-sweats, coughs almost constantly, and there is not a normal respiratory sound to be heard in any portion of her lungs.

Now, I wish to ask, When should the treatment for tuberculosis have been begun in this case? Did the *grippe* of March, 1896, develop the tuberculosis? What caused the loss in flesh so plainly recognized in August, 1895? What caused the daily chilly sensations and the afternoon fever at that time? Are

not the chances ten to one—yes, one hundred to one—that she was tuberculous then? Are we to wait until the bacillus grows vigorously and lung tissue begins to break down before we even suspect the existence of a disease so frequently present that it destroys one-seventh of the race? Does the surgeon wait until the inflammed appendix ruptures and every doubt of the nature of the trouble is removed by the collapse of the patient before he operates? If he did this, would the operation statistics for appendicitis be as favorable as they now are? I have no doubt that a healthy appendix is sometimes found by the operator, and it might happen, did we not wait for the appearance of the bacillus, that some non-tuberculous person would be treated for that disease, but the operation, skilfully done, does not kill, nor would the treatment for tuberculosis do harm. In many cases tuberculosis can be recognized before the bacillus appears in the sputum, with as much certainty as appendicitis can be diagnosed before rupture occurs.

Have we not a well-known method for the recognition of malaria when it has a real existence? Have we not in quinin, the one specific known to scientific medicine, a test for malaria? We have these, but we do not take the trouble to examine a drop of blood from the finger for the plasmodium, and although quinin fails to prevent the daily return of the afternoon "flush," we excuse our neglect, console our patients, and give the bacillus tuberculosis ample time to destroy the lungs, while we fire our quinin pills and capsules at a phantom.[1]

[1] It is an interesting fact that malaria was once regarded as an-

The physician who desires to recognize tuberculosis in its earliest stages must take into consideration all the known signs and symptoms of the disease. In one instance the bacillus may appear in the sputum early, in another late, and in a third not at all. In our reliance on the detection of the bacillus, we must not neglect the evidence which we may gain by auscultation, by percussion, by carefully watching the temperature, etc. I will put in condensed form my ideas concerning the means which should be employed in the early recognition of tuberculosis:

1. Whenever there is any sputum it should be examined for tubercle bacilli. If the bacilli are not found in the first examination the search for them is to be repeated. When the bacilli are present the diagnosis of tuberculosis is positive. Failures to find bacilli, even after repeated examinations, does not prove the absence of tuberculosis. The complete absence of cough and of sputum is not proof of the non-existence of tuberculosis.

2. Apical catarrh, even when no bacilli are found in the sputum, is in the great majority of instances due to tuberculosis. Leube is certainly right when he says: "Marked dulness of the percussion note over the apex is always ('fast immer') a symptom of pulmonary tuberculosis, especially when the dulness is unilateral, and is detectable also in the infraclavicular fossa or in the regio supraspinata. . . . Still more certain is the diagnosis when the dulness on

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tagonistic to tuberculosis. This view was especially championed by Buffalini and other Italians, and this supposed antagonism was cleverly used by Brehmer in explaining his theories. See "Die Gesetze und die Heilbarkeit der Chronischen Tuberculose der Lunge," Berlin, 1856.

percussion is accompanied by auscultatory variations from the normal. The slightest variations in the respiratory sounds suffice here, such as jerky breathing, prolonged expiration, feeble or intensified, or rough vesicular breathing, and indefinite respiratory sounds. If the breathing be of bronchial character, or if there be râles, even when these are isolated, the slightest percussion dulness in the apex becomes of great diagnostic significance."

Among the very earliest variations in respiratory sounds in tuberculosis is a prolonged expiratory movement. When this is accompanied by retraction of the apex and dulness on percussion, there can be but little doubt about the diagnosis. This prolongation of the expiratory sounds is so easily and so certainly recognized and its diagnostic value is so great that I wish to emphasize this mention of it.

There is a tendency among medical men at present to pronounce no disease of the lung tuberculous unless the bacillus is found in the sputum. I had myself fallen for awhile into this error. Such cases as the following lead me to believe that this is an error:

P., now aged fifty-six, had consulted me occasionally for years. As early as 1893 he began to lose weight and to complain of weariness upon slight exertion. This decrease in weight has slowly continued. During the winter of 1894–95, he had frequent and persistent colds, during which he coughed up mucus. There was at that time only a prolonged expiratory sound over the right apex and subclavicular region. The sputum was examined during these colds, but always with negative results. In the fall of 1895, he returned from his vacation with a well marked apical catarrh on the right side. The sputum

was examined repeatedly during the following winter, but again negatively. On account of the failure to find the bacilli, the nuclein was not employed. In September, 1896, he returned from a three-months' vacation with a cavity under the clavicle on the right side, with the left upper lobe involved and his sputum laden with bacilli.

3. I will again quote from Leube as follows: "It has recently become more and more certain that the apparently spontaneous pulmonary hemorrhages which occur in those supposedly well are not causes of tuberculosis, but are the results of a disease already established." The teaching of Niemeyer[1] that pulmonary hemorrhage is a cause of tuberculosis was founded upon erroneous ideas of both the etiology and pathology of the disease and should have been discarded years ago. I have already called attention to the desirability of examining the blood for tubercle bacilli in every case of pulmonary hemorrhage. The germs will not always be found, even when the hemorrhage is of tubercular origin, as it is in the great majority of instances, but when they are found there can be no longer any doubt about the nature of the lesion. I have seen so many cases in which the golden opportunity for beginning proper treatment, medicinal or climatic, has been indicated by hemorrhage, the warning has been disregarded, and the disease has next manifested itself in a grave form, that I desire to briefly report one such case:

A young lady of eighteen had in February, 1895, a slight hemorrhage and continued for some days to cough up blood. A physician pronounced it vica-

[1] "Klinische Vorträge über die Lugenschwindsucht," 1869.

rious menstruation, finding some reason for this in the fact that the monthly flow had been somewhat scanty. The young lady began to cough late in the spring of 1896, and an examination of the lungs in July of this year showed dulness over both upper lobes, bronchial breathing with bubbling râles, a small cavity in the left subclavicular area, and an extensive pleuritic effusion over the lower half of the right lung. The sputum contained innumerable pin-head tubercles, and these crushed between cover glasses and stained were found to be full of bacilli.

Now, can any one with the subsequent history known doubt that this patient was tuberculous in February, 1895? With instances of this kind coming under professional observation constantly it does seem that we should interpret the significance of early hemorrhage more correctly.

The studies of Rindfleisch have made us acquainted with the pathology of hemorrhage in initial tuberculosis. The tubercular process extends into the wall of the artery destroying the media and at times the intima, thus forming a spot where the rupture occurs. Fortunately this usually happens in one of the very small end arteries, and the hemorrhage is consequently slight. According to Rühle, late hemorrhages are of somewhat different origin and are more likely to be serious. Here the arteries in the walls of cavities, being left unsupported by the destruction of the adjacent tissue form aneurismal sacs which break.

There is considerable difference of opinion among the authorities concerning the effects of hemorrhages in pulmonary tuberculosis upon the temperature. Ac-

cording to Wunderlich,[1] Lebert,[2] and Schwarz,[3] even slight hemorrhages in any and all stages of the disease are followed by at least a temporary depression of temperature. While Niemeyer[4] and Uhrig[5] state that hemoptosis is usually followed by an elevation of temperature, and Simonsohn,[6] that there is no uniformity in the effects, I wish to state in this connection that when a supposedly healthy person has come to me on account of pulmonary hemorrhage I have always found at some time of the day, usually in the afternoon, an elevation of temperature. Of course I cannot say whether these persons were febrile before the hemorrhage or not.

4. It is stated by good authorities that some cases of pulmonary tuberculosis run their entire course without any elevation of temperature. I have never seen such a case. I fail to find any such case reported in sufficient detail to justify me in believing the statement to be true. When the temperature is taken only morning and evening, the record may show no elevation; especially is this likely to be true when the evening record is made late. However, this is not the correct method of taking the temperature in this disease. The maximum temperature is, in the great majority of instances, in the afternoon, and not in the evening. My experience leads me to believe that the temperature curve of

[1] "Eigenwärme in Krankheiten."
[2] "Veranderungen der Korperwarme im Laufe der Tuberculosis."
[3] "Ueber den Fieberverlauf bei Phthisis pulmonalis."
[4] "Klinische Vortrage über die Lungenschwindsucht."
[5] "Welchen Einfluss hat das Blutspeien auf die Temperatur bei Phthisis," 1885.
[6] "Hat das Haemoptoe einen charakteristischen Einfluss auf die Temperatur," 1887.

tuberculosis is as characteristic as that of typhoid fever; and, indeed, there are fewer variations than in typhoid. While there are exceptions and while exercise often markedly alters the temperature of a given hour, the rule holds that the maximum is between three and six P.M. The record should always be made at eight A.M., twelve M., four P.M., and eight P.M. When this is done the maximum will, in the majority of instances, when averaged for a week, be at four P.M.

In acute miliary tuberculosis the temperature curve is very irregular and my observation confirms the statement of Rühle[1] who says: "The irregularity of the fever curve of miliary tuberculosis is of importance in distinguishing it from other febrile diseases from which it otherwise might be confounded."

It would seem to be superfluous to say that but little reliance can be placed on the patient's statement that there is no fever. However, I have this day received a letter in which a physician writes substantially as follows: "Mrs. A. has been tuberculous for two years. She states that she has been free from fever, but I find that since I began the nuclein her afternoon temperature sometimes goes as high as 101° F." In all cases it is well to have a temperature record for a week before treatment is begun.

Burkhardt, working under Strumpell, has written a monograph on the temperature in tuberculosis.[2] This monograph is a good illustration of the careless mannner in which the temperature in tuberculosis has been studied even in some of the most renowned

[1] "Die Lungenschwindsucht und die Acute Miliartuberkulose." Ziemssen's *Handbuch*.

[2] "Ueber das Verhalten der Eigenwarme bei der Lungentuberculose," 1891.

clinics. Burkhardt makes five classes of temperature curves in tuberculosis:

(1) Afebrile, both in the beginning and during the course of the disease. (2) Subfebrile: "In a large number of cases the morning temperature is (zwar) normal, while the evening temperature shows a slight elevation (from 38° to 38.5° C.)." (3) Hectic fever: "The morning temperature is normal, while the evening temperature goes to 39° or 39.5° C." (4) Continued fever (Volliges Verschwinden normaler Eigenwärme). (5) Irregular temperature (Grosse Unregelmässigkeit des Wärmeganges).

5. Loss of weight is practically a constant and frequently an early accompaniment of tuberculosis. However, before any significance can be attached to loss of weight in our endeavor to make an early diagnosis, other causes of the loss must be excluded. Loss of weight, when coupled with the characteristic temperature curve furnishes very strong presumptive evidence of the existence of tuberculosis in some part of the body. Much has been said about a "pretubercular" condition, in which there is a decrease of weight, a sensation of general weariness, and loss of appetite, and which is supposed to render the person especially susceptible to tuberculosis. It is in these cases that an attack of influenza, measles, whooping-cough, pleurisy, pneumonia, or a "bad cold" is so frequently supposed to be the starting point of consumption. The physician recognizes this so-called "pretubercular" condition. Sometimes he administers iron, quinin, and other tonics, and thus tries to prepare the patient for the disease to which he is supposed to be specially susceptible,

and I am by no means ready to deny that this treatment is beneficial. However, the mistake is made in looking upon this condition as "pretubercular;" it is tubercular, and the time to treat it is before the tuberculosis becomes a mixed infection by the advent of some intercurrent disease.

In taking the weight it is well to use the tables of Quetélet[1] or some modification of the same as a basis of comparison. Conradi[2] has given us a valuable paper on the decrease in body weight in tuberculosis, and he has pointed out the fact that decrease in weight is important evidence of the disease in its early stages. This decrease is due to want of assimilation; later, it may be in part due to fever. Conradi has pointed out the following facts: (1) The decrease in weight is greater in proportion to the prostration accompanying it than in most diseases. (2) The younger the patient the greater will be the loss in weight necessary to induce prostration. (By prostration the author here means inability, from weakness of the patient, to attend to his ordinary duties.) (3) After prostration decrease in weight continues, but, as a rule, not so rapidly.

Besides the above-mentioned evidences of tuberculosis there are many other conditions which should lead us to suspect the existence of this disease. Although thirty years have passed since Flemming[3] showed that pleurisy is due in a large per cent. of the cases to coexisting and preexisting tuberculosis,

[1] "Sur l'homme et le development de ses facultes."

[2] "Ueber das Korpergewicht des Menschen und die Abnahme bei der Tuberculose." Leipzig, 1843.

[3] "Ueber die Häufigkeit der Combination von Pleuritis und Tuberkulose und das Abhängigkeitverhaltniss beider Krankheiten von Einander," Weimar, 1876.

the profession has given but little attention to this matter, and attack after attack of pleurisy in the same individual is treated, while the tuberculosis, which is the cause of the pleurisy, is never thought of until the lungs are practically destroyed.

In 106 *post-mortems* Schlenker[1] found the pleura normal in twenty-one bodies (19.8 per cent.); pleura diseased in eighty-five (80.2 per cent.). The pleurisy was associated with extensive tubercular changes in the lungs in twenty-eight (26.4 per cent.); with latent tuberculosis of the lungs or bronchial glands in thirty-three (31.1 per cent.). There was tuberculosis without pleurisy in four (3.4 per cent.); and pleurisy without tuberculosis in twenty-four (22.6 per cent.). The author states that if tubercular lesions had been sought for microscopically the number of cases of pleurisy without tuberculosis would have been decreased..

I have come to believe that when physicians acquire and practise in the diagnosis of tuberculosis a degree of skill equal to that employed by surgeons in the recognition of appendicitis, pulmonary tuberculosis will be detected in its earliest stages; and when this is done it will be placed among the most easily curable of the graver infectious diseases.

[1] "Beiträge zur Lehre von der menschlishen Tuberkulose." See *Deutsche Med. Wochenschrift*, 1883, Nos. 31 and 32. Also Virchow's *Archiv.*, B. 108, S. 233.