Wilcox (R. W.)

THE TREATMENT OF PULMONARY TUBERCULOSIS

BY

HYPODERMIC INJECTIONS OF NUCLEIN.

BY

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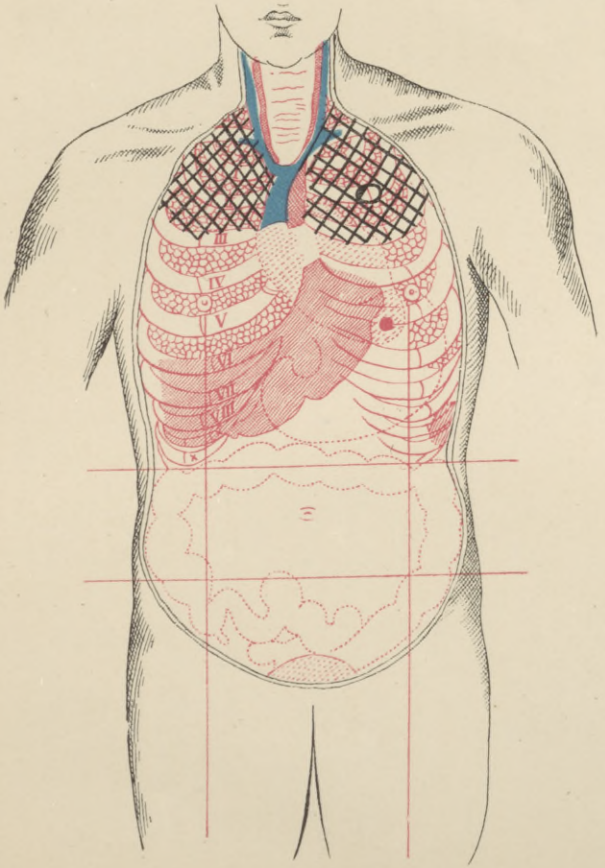
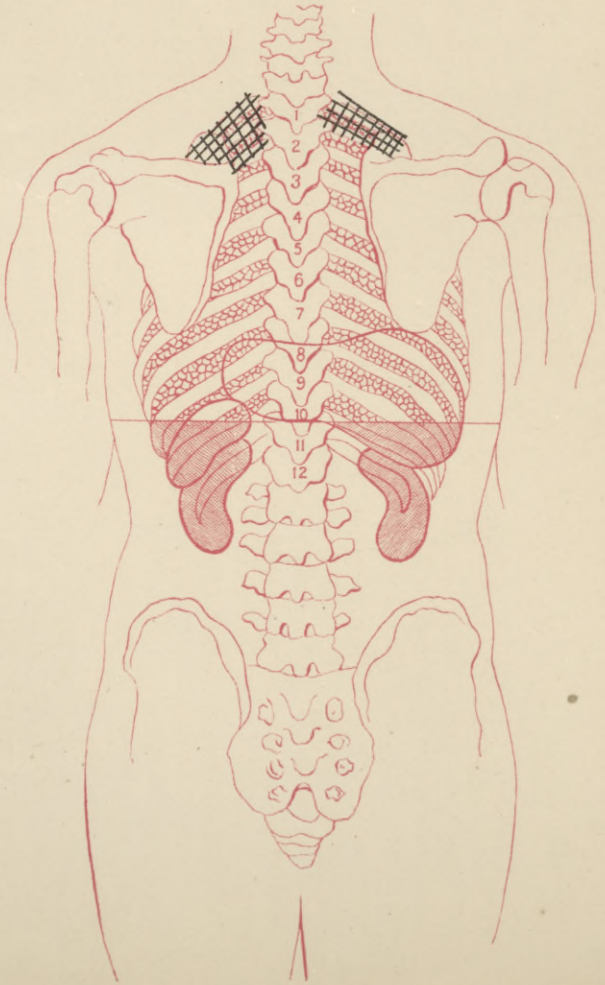
Anterior aspect of trunk (after Weil-Luschka).



Posterior aspect of trunk (after Weil-Luschka).



THE TREATMENT OF PULMONARY TUBERCULOSIS BY HYPODERMIC INJECTIONS OF NUCLEIN.

THE question of to-day is, without doubt, the treatment of infectious diseases by substances derived from organic bodies. The two methods employed are (1) the use of substances believed to neutralize the toxins resulting from bacterial life,—that is, the antitoxins,—and (2) the use of substances which will assist the natural processes in resisting the effect of bacterial infection,—that is, the defensive proteids, the alexins. The former may be and undoubtedly are dangerous; the latter are harmless. Taking as a type of the first class antitoxin, there come before our recollection the observations of Landois, Darenberg, Hayem, and Lozet, that an alien serum—a serum transfused into the blood of an animal of another species—will dissolve blood-corpuscles, produce small emboli, which consist of the degenerated elements of the blood, the hæmatoblasts, the red and white corpuscles, and even produce congestion of the kidneys and suppression of the urine. That this may and does take place is shown by the reports of Lennox Browne, of Benda, and inferentially by Winters in a most scholarly address recently delivered before the New York Academy of Medicine. That antitoxin of itself may produce septicæmia in its various forms, rashes, joint pains, and even death itself, there can be no reasonable doubt. That it does more than neutralize the toxin produced by the Klebs-Loeffler bacillus is not claimed, and that it antidotes other infections than that just mentioned cannot be maintained. That it is not preventive when administered to a healthy individual is demonstrated by the cases reported by Koesel and Goebel. So much for the typical antitoxin, a representative of the first class.

Taking nuclein as a representative of the second class, we have a substance easily obtainable from the spleen, bone marrow, thyroid and thymus glands, eggs, testes, blood, brain-substance, and from yeast. Thus far no untoward result has been produced by its internal administration; it is safe. We may follow Vaughan in describing it as "that constituent of the cell by virtue of which the histologic unit grows, develops, and reproduces itself." It utilizes the pabulum within its reach. It is a complex, proteid body, especially rich in phosphorus, which exists in the form of nucleinic acid, combined with a highly complex basic substance, which may yield, as decomposition products, adenin, guanin, sukin, and xanthin. The nucleins are generally insoluble in dilute acids, soluble in dilute alkalies, and resist peptic digestion. It is unnecessary to review the literature of the subject,—the work of Braconnet, Knapp, Quevenne, Schlossberger, Geoghan, Mitscherlich, Béchamp, Miescher, Althouse, Hoppe Seyler, Liebermann, Lubavin, Plösz, Kossel, Altmann, Malfatti, Sée, and Horbachzewski,—since this has recently been so carefully done by Vaughan in his able address before the Illinois State Medical Society. The practical side of the question has received careful attention at the hands of McClintock, Garber, Bleyer, Knapp, and Aulde. What, then, can we hope to obtain from the administration of this remedy? Vaughan and McClintock, after a careful study of the literature on the subject and from their extensive investigations, conclude (1) that the germicidal substance in blood-serum must belong to the proteids, and (2) that the only proteid likely to be present in blood-serum, and which is not destroyed by peptic digestion, is nuclein. Further, they demonstrated that blood-serum contains a nuclein, and that this nuclein possesses a germicidal action. Their experiments were upon the bacillus of Asiatic cholera, staphylococcus pyogenes aureus, and anthrax bacillus without spores. The nuclein obtained from yeast—about two-per-cent. solution—protected rabbits and guinea-pigs against virulent cultures of the diplococcus of pneumonia. The immunity thus secured was not directly due to the action of the nuclein as a germicide, but probably depended upon its stimulative effect upon some organ whose function it is to protect the body against bacterial invasion. So far as the tubercle-bacillus is concerned, the authors conclude that the progress of tuberculosis in guinea-pigs after inoculation was retarded and the virulence of the germ reduced by the treatment by nuclein.

For the treatment of infectious diseases we

must look either (1) to non-poisonous germicides of cellular origin, or (2) to substances which stimulate the activity of those organs whose function it is to protect the body against those diseases. Metchnikoff taught that the polynuclear white corpuscles were the natural defenders against bacterial invasion. Vaughan and McClintock have shown that the germicidal substance in blood-serum is a nuclein, and that the most probable source of this nuclein which is found in blood-serum is the polynuclear white corpuscle. Huber has shown that the subcutaneous injection of nuclein increases the number of white blood-corpuscles in both healthy and tuberculous individuals, even to three times the original number. This increase occurs principally in the polynuclear cells, and is evident as early as the third and generally disappears after the forty-eighth hour. Even if the researches of Nuttal, which tend to disprove the theory of Metchnikoff, be accepted, the force of the argument for the use of nuclein in infectious diseases is not impaired. That others have sought to invoke the aid of these same white corpuscles in the cure of tuberculosis is evident if we study the work of Liebreich on potassium cantharidinate and of Waldstein on pilocarpine. That this method—the use of nuclein—offers greater probability of success is evident when one considers that, as compared with both of those substances above mentioned, it is harmless. Further, if it is true that the red blood-globules have for their antecedents the white corpuscles, we have in nuclein an excellent means of combating the profound anæmia which marks the systemic invasion of a contagious disease.

The clinical reports now cover its use in amygdalitis, membranous and follicular tonsillitis, malarial disease, indolent ulcer of the leg, myxœdema, neurasthenia, diphtheria in its various forms, tuberculous adenitis, and pulmonary tuberculosis. It is chiefly concerning the last-named disease that my interest has been awakened.

During the past ten years I have investigated in my clinic every method which has been advanced for the treatment of pulmonary tuberculosis. The value of each has been arrived at after months of patient investigation of clinical history, repeated physical examinations, and careful bacteriological study. It was with a scepticism born of repeated disappointments that I commenced the use of nuclein. The basis of reasoning being in this case so entirely different from that usually adduced by the advocates of the various "cures," I was led to undertake an extensive investigation. Most of the observations having been made upon dispensary and hospital patients, who promptly disappear as soon as their symptoms are relieved, it is difficult to keep them sufficiently long under observation for a complete report. The following patient certainly promised little, yet the result was very satisfactory. The following is the report:

A. P., a native of Russia, twenty-four years of age, by occupation an agent, was admitted to St. Mark's Hospital, November 29, 1894.

Previous History.—Family history is negative. The patient was always well until eight months ago, when he began to have a slight cough, but without noticeable expectoration. Six months before admission expectoration began to accompany his cough, the expectorated material being at times bloody. He soon was relieved of these symptoms by treatment, and thought that he was well until three days before admission, when he again began to cough and to raise bloody sputum. He has had several very free hemorrhages from his nose and mouth, which are usually begun by coughing. For five weeks his voice has been quite hoarse and his throat has given him discomfort. He has lost some flesh, but the extent of emaciation cannot be stated. His strength has also become impaired. No symptoms of digestive disturbance have been noted.

Present Condition.—He is now suffering from some pain in the upper part of both lungs, although previously he had but little. He is troubled with dyspnœa. His cough is frequent, causing loss of sleep, and accompanied by a muco-purulent expectoration which contains clots of blood. Physical examination shows him to be a man of fairly good weight. His lips and skin are pale. His pulse at 9 P.M. is 110, of good volume, easily compressible, and regular in rhythm. His temperature is 101.2° F., respiration 28. Inspection of his chest shows it to be of good antero-posterior diameter, but with some sinking in of both supraclavicular regions; the depression below the clavicle is less, though more noticeable upon the left side. The superficial reflexes are exaggerated and myoidema is obtained at both apices. On the right side there is a high-pitched, shortened percussion-note with distinct dulness, which extends to the upper border of the third rib in front to the extreme top of the axillary region, and behind to the upper border of the spine of the scapula. Over this area both inspiration and expiration are prolonged and of higher than normal pitch, and distinctly rough in character. Within the limits above outlined are heard many crepitant râles at

the end of inspiration, together with small, tenacious, and larger mucous râles on both expiration and inspiration. Vocal resonance and fremitus are increased. On the left side there is a high-pitched, shortened percussion-note, with nearly absolute flatness extending to the lower border of the third rib in front, a finger's breadth below the apex of the axillary region and two fingers'-breadth above the spine of the scapula, behind. For a small space over the middle of the anterior half of the second rib is found a distinct vesiculo-tympanitic percussion note. Over this area the inspiration is prolonged, of higher pitch than normal, and of tubular character. The expiration is not changed in duration, but is of slightly higher pitch. Within these limits are heard many crepitant râles, chiefly at the end of inspiration, together with a few small mucous râles. Vocal resonance and fremitus are increased. Over the site of the vesiculo-tympanitic percussion-note the expiration is of lower pitch, prolonged, and of musical quality. The area of cardiac flatness and the position of the apex beat is normal. The first sound is of somewhat shorter duration, but of good pitch and quality; the pulmonic second sound is accentuated.

Diagnosis.—Pulmonary hemorrhage in the upper lobe of the right lung due to an infiltration of presumably tuberculous origin, with resulting acute catarrhal bronchitis. On the left side an infiltration of presumably tuberculous origin, resulting in a dilated bronchus, involving the upper portion of the upper lobe of the left lung and at present quiescent.

Treatment.—1 drop of Fleming's tincture of aconite root every two hours, alternating with 15 drops of aromatic sulphuric acid in which is dissolved 2 grains of quinine sulphate, until the hemorrhage shall cease. The bowels are to be moved every day, if necessary, and the diet is to be exclusively of milk.

Further History.—The hemorrhage ceased upon the following day, and the interval between the doses of medicine was increased to four hours.

December 3.—The temperature is at 8 A.M. 100.6° F.; the pulse is 84, regular, and of fair volume and tension; the respirations are 23. The blood has now disappeared from the expectoration, which is profuse, watery, and purulent, with masses settling to the bottom of the cup. Microscopical examination shows it to contain innumerable tubercle bacilli.

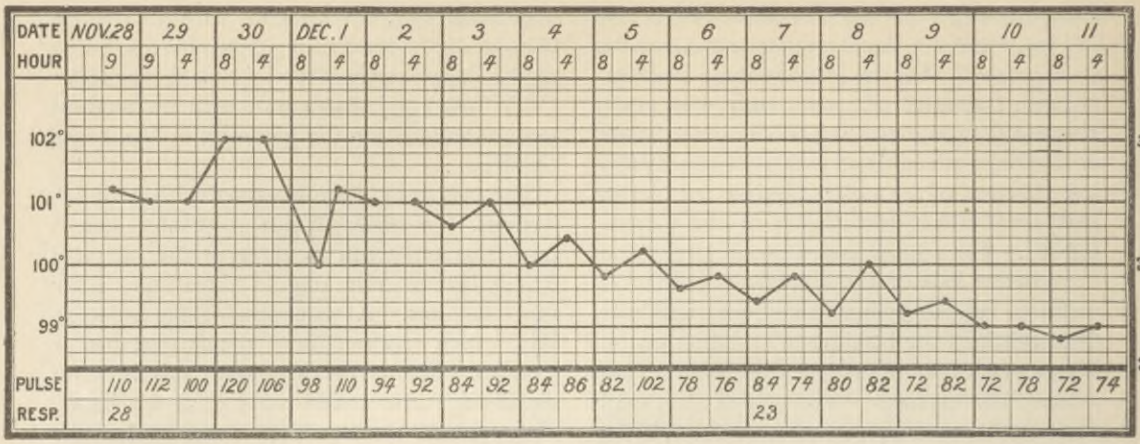
December 4.—All medication is now omitted. The patient is to receive the regular house diet; the bowels, if necessary, to be moved as before. Nuclein, which was furnished me by Parke, Davis & Co., was now ordered to be given hypodermically, commencing with 10 minims twice daily, and increasing 5 minims each day until a daily dosage of 80 minims is reached.

The following observations and instructions were submitted for the guidance of the house physician:

The best results are obtained with daily injections. In some patients a rise of temperature from one-tenth to three or four degrees may follow in from one to three hours after the injections. A numbness of the adjacent skin, which may run down the nearest arm or leg, often follows the injection; this is of no significance and passes away in a few hours. The pain of the injections becomes less the oftener they are repeated. The locality in which the injections are made seems to make but little difference. It will generally be found most convenient to give the injections in the muscles of the back or the upper part of the chest. If the patient is quite thin, the injections are less painful when made in the gluteal region. The pain is less if the needle is thrust deep into the muscles rather than subcutaneously. The larger nerves and blood-vessels are, of course, to be avoided. In giving large quantities of fluid hypodermically there is always danger of induration and abscess. To avoid them, observe the following precautions: The syringe must be daily washed with five per-cent. carbolic acid, followed by boiling water. The needle should be kept in a small dish of five-per-cent. carbolic acid, and should be kept sharp. The spot where the injection is to be made should be thoroughly washed with the five-per-cent. carbolic acid solution. This disinfects the skin and also acts as a local anæsthetic, diminishing the pain of the injection. To get the nuclein into the syringe it will be found convenient to have a small dish or beaker. This should be sterilized in the same manner as the syringe. Pour into this small dish the amount of nuclein to be used and then draw into the syringe. Keep the syringe, needle, small dish, and bottle of nuclein in some dust-free receptacle. A syringe holding eighty minims is much more convenient than a smaller one, which must be refilled several times.

December 16.—The maximum daily dosage of 80 minims has now been reached. No elevation of temperature following the injections has been noticed. On the 9th an induration followed one injection, probably due to uncleanliness of the needle; this had disappeared by the 13th. At 8 A.M. the temperature was 98.4° F., the pulse 70, full, and regular, and

TEMPERATURE CHART I.—A. P.



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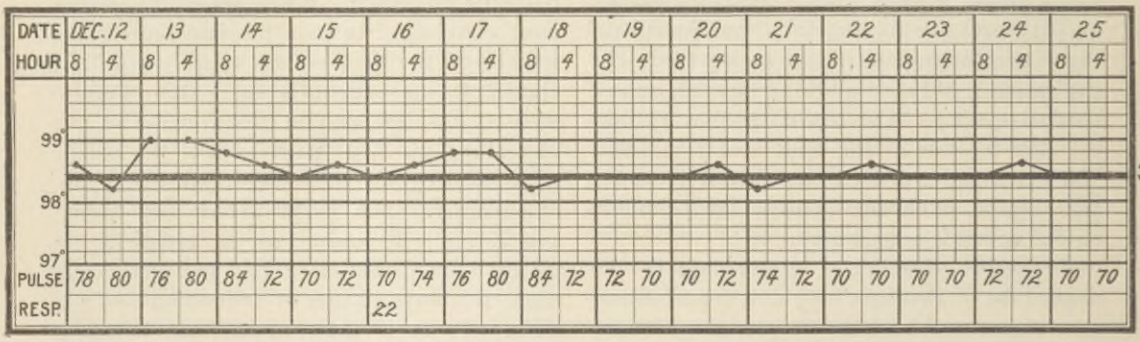

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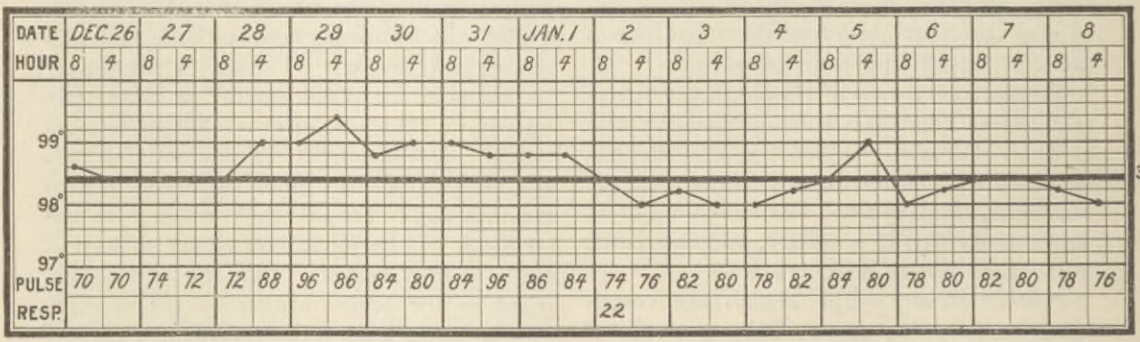

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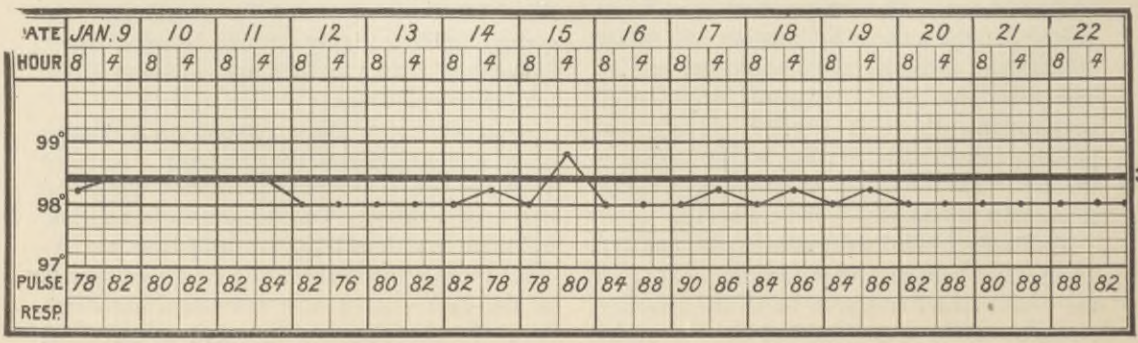

the respirations 22. Physical examination shows that while the dulness, increased vocal resonance and fremitus, respiratory changes, and crepitant râles still remain on the right side, all other signs have disappeared. On the left side the râles are fewer and the dulness less marked. He has gained in flesh, is in better spirits, and his dyspnœa has entirely disappeared. The cough is much lessened in frequency, and is accompanied by a muco-purulent expectoration, of which, however, the quantity is lessened.

January 2, 1895.—The maximum daily amount of nuclein has been continued. The expectoration is still muco-purulent, and although from its appearance it promised well, no tubercle-bacilli were found on careful examination. The temperature is now at 8 A.M. 98.4° F., the pulse 74, of good volume and tension, and the respiration 22. The patient's general condition is improving, and the dulness becoming less marked upon the right side and the râles still fewer.

January 14.—The expectoration is gradually lessening in amount, and no tubercle-bacilli could be found on careful examination.

January 23.—At 8 A.M. to-day his temperature is 98° F., the pulse 82, of good force and volume, the respiration 22. The physical signs have markedly improved, and although the crepitant râles are still present, the dulness is very much lessened, and the general condition is good. No tubercle-bacilli can be found in his expectoration.

January 30.—Improvement has steadily continued, not only as to general condition, but the cough and expectoration have diminished, and the patient feels well enough to resume work.

February 1.—The patient reported at my clinic at the New York Post-Graduate Medical School. He was directed to take the syrup of lime hypophosphite, 1 drachm in a wineglassful of water after each meal.

February 15.—No tubercle-bacilli were found on examination, with one-twelfth oil-immersion Leitz lens. His general condition is improving.

"*June 13.*—No subsequent examinations have been made, owing to the fact that he disappeared from the clinic and I have been unable to find him."—*Report of Clinical Assistant.*

Since the patient was very anxious to resume his work, it is probable that he has continued in fair health. He is sufficiently intelligent, etc., to return; had his health become impaired he would doubtless have reported.

The results obtained in this patient certainly are striking. That the bacilli disappeared from the expectoration during his stay in the hospital is not wonderful, for all know what may be gained by cleanliness, rest, pure air, and a nourishing diet; but when he had returned to his former abode and the benefits of hospital residence were denied him, that they did not return during the time that he was under observation is a fact clearly showing the durability of the effects of the remedy. The results are confirmed by the recent observations of Tiegen, who reported benefit in two out of four patients.

The beneficial results which have been obtained may be explained partly (1) because nuclein increases the vigor of the central nervous system (Bleyer), (2) that it has germicidal properties (Kassel), or (3) that its use results in the production of polynuclear corpuscles (Vaughan). He believes that it stimulates the organs which elaborate these bodies. Thus far its use has not been attended by toxic manifestations, but it is quite within probability that overstimulation might be brought about. The remedy may fail through this overstimulation, producing a paralysis of function, or the organs which produce the above-mentioned corpuscles may fail to respond because of their lowered vitality.

In what cases may we expect benefit? Evidently in early cases of limited tuberculous infection only, in individuals of fair general health, we may look for a cure with reasonable certainty. The disease may be retarded even if cavity formation is evident; it may even become quiescent. The cases which present secondary infection from pyogenic germs, extended area of involvement, debilitated, broken-down individuals, long-standing illness, or with frequent acute exacerbations, offer much less hope of producing amelioration; unfortunately, these are the very patients who expect the most of us and our remedy. Even here we may hope for better results than from any other method at present known to medical science. The source of nuclein (yeast) precludes any anxiety as to the limitation of the supply; we are not even interested in the artificial product prepared by Liebermann from albumin and metaphosphoric acid.

What, then, may we say in conclusion? I believe it to be true (1) that nuclein is absolutely harmless; (2) that it assists nature in limiting the effects of bacterial invasion; (3) that it offers, in comparison with other "specific" methods, the best prospects of success in the treatment of pulmonary tuberculosis.

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