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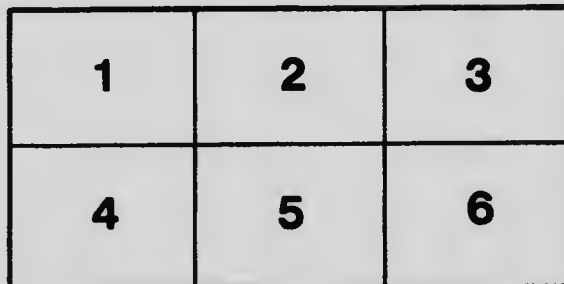
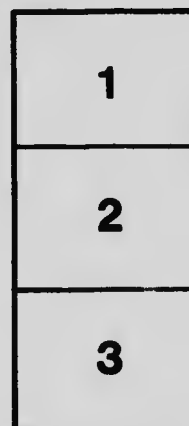
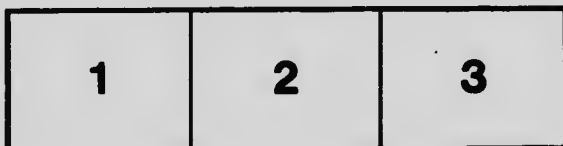
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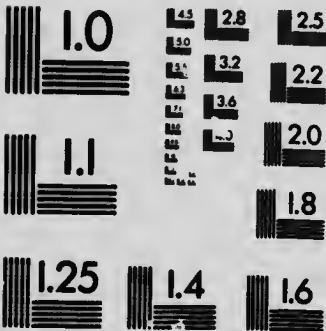
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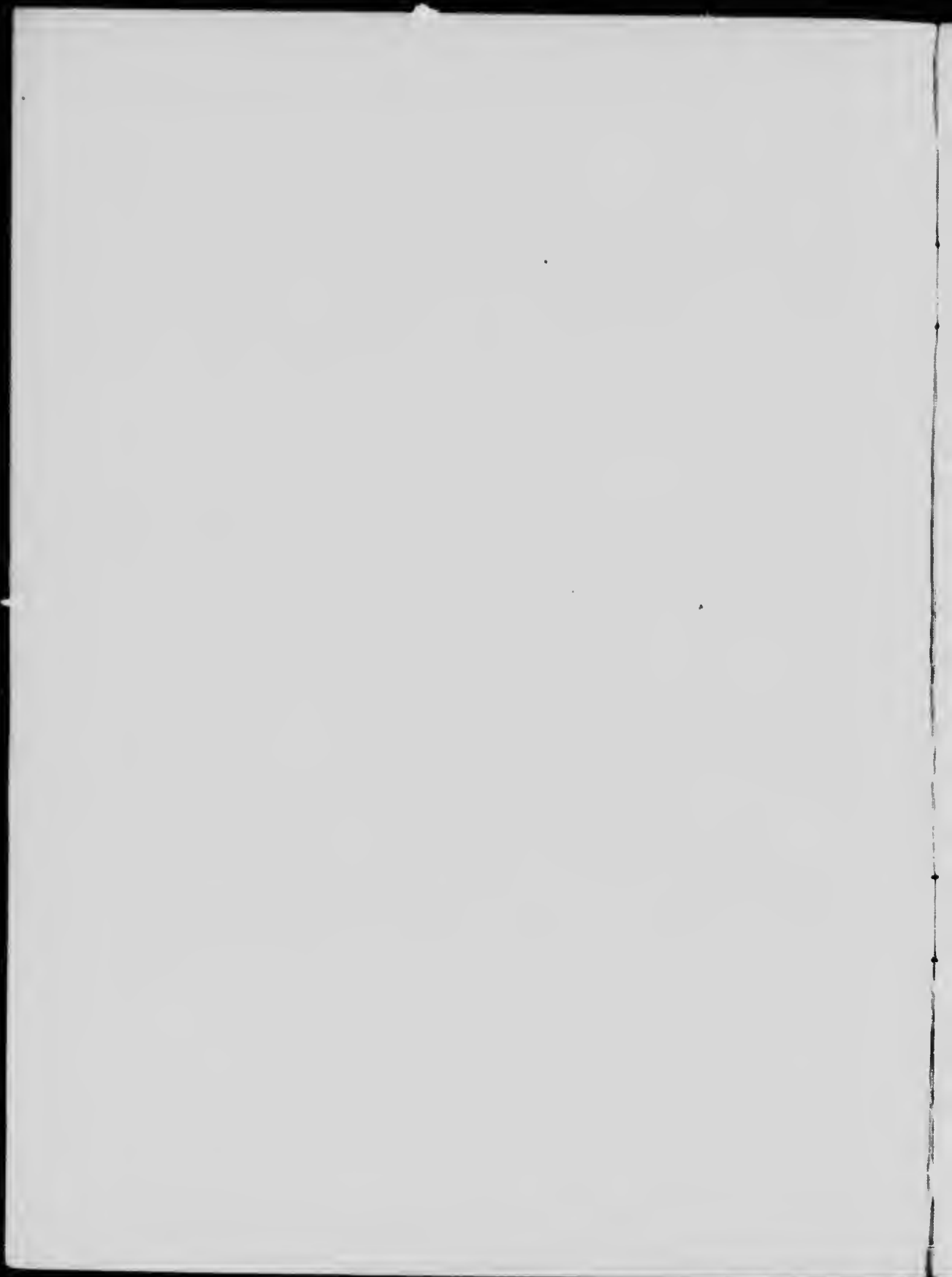
1653 East Main Street
Rochester, New York 14609 USA
(716) 482 - 0300 - Phone
(716) 288 - 5989 - Fax

THE PREVENTION OF TUBERCULOSIS

BY
J. H. H. H. H.

THE LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE
LONDON
1910

CEBR-5



THE PREVENTION OF TUBERCULOSIS

BY

SAMUEL G. DIXON, M. D.

OF PHILADELPHIA

*President of The Academy of Natural Sciences of Philadelphia ;
Commissioner of Health of the Commonwealth
of Pennsylvania*

Read before the Section of State Medicine
of the British Medical Association
at Toronto, Canada
August 21, 1906



THE PREVENTION OF TUBERCULOSIS

SCIENCE knows no limitation of race, language or geography. The earnest scientist rejoices in the discovery of every new truth, whatever the nationality of the patient searcher who was so fortunate as to unearth it. On the other hand, the discoverer is willing and eager to share his newly acquired knowledge with his fellow investigators throughout the broad domains of the earth, regardless of nationality or birthplace. If this is true of science in general, it is true in a greater degree of our own beloved science of medicine. By the devotees of no other is the grand conception of the brotherhood of man so completely and so practically recognized.

Especially has the growing custom of holding medical and hygienic conventions, conferences and congresses in the various great cities and scientific centres of the world, thus affording members of the profession opportunities for personal as well as literary intercourse, contributed to the strengthening of this *entente cordiale*.

This is the second time that this association has met on American soil, and again it holds out a hand of kindly greeting to its brethren across the imaginary line which separates two great nations, distinct indeed politically, but one in all that constitutes unanimity of sentiment, harmony of aspiration toward a nobler and truer life, and community of labor for the advancement of medical science, and hence of humanity at large.

I appreciate the courtesy extended to me in having been requested to appear before this distinguished body, and to contribute my humble mite towards the great treasury of knowledge which it is constantly amassing.

Nine years have elapsed since your last assembling on this continent. In that brief space of time what changes have taken place!

The science of bacteriology, then comparatively in its infancy, has taken its place as one of the most important departments of medicine. Serum-therapy, then cherished by but a few enthusiasts, the butt of crass medical wits, has established itself firmly as a therapeutic method of no uncertain value. By its means it has been found possible not only to prevent the spread of some of the most serious communicable diseases to a considerable extent, but also to greatly lessen their mortality.

In March, 1882, came the startling announcement of one of the great masters in bacteriology—Koch—that he had discovered the micro-organism of the tubercle. This announcement was received with acclamation throughout the scientific world, for it held out a hope that, through the means of this discovery, a possibility might have been created of checking the ravages of a disease which was responsible for the destruction of human life to a far greater extent than any other.

The years slipped by, however, and no sign was given from any of the great laboratories of the world. In the summer of 1889 I visited London to study the technical methods used in the bacteriological laboratories of King's College and the College of State Medicine. While working in Professor Klein's College, I was staining a smear of tubercle bacilli which had been kept in a tube from an incubator to which the students had free access; the temperature, therefore, was by no means constant. At first club-shaped bacilli developed; then gradually, the tube having been allowed to remain at the temperature of the room for several hours out of the twenty-four, for a few days considerable variations from the form heretofore recognized were disclosed to my astonished eye.

The impression made upon my mind was a profound one. I felt convinced that the irregularity in growth might properly be designated as an involution form. Some of these forms were club-shaped, some curved, and some branched. Did they not represent bacilli of attenuated virulence and reduced strength? If so, might they not be availed of in establishing a tolerance for the tubercle

bacillus in animals and even in man? The more deeply I pondered over this discovery, the more thoroughly was I convinced that there was a valuable truth concealed in it. On my return to America I immediately instituted a series of experiments, with the result that I was able to produce a less virulent culture than had hitherto been recognized. I felt no hesitation, therefore, in giving these results to the public, which I did in the columns of the *Medical News* of Philadelphia in a memorandum entitled "Possibility of Establishing Tolerance for the Tubercle Bacillus." This article appeared on October 19th, 1889, and was accompanied by a cut representing tubercle bacilli in other forms than those before recognized. I then said:

"In considering a means for overcoming infection by tuberculosis, it is possible that a condition of tolerance to the action of the tuberculous bacillus must first be established. To this end two hypotheses may be suggested:

"First. It is possible, that by a thorough filtering out of bacilli from tuberculous material a filtrate might be obtained and attenuated so that by systematic inoculations a change might be produced in living animal tissues that would enable them to resist virulent tubercle bacilli.

"Secondly. To bring about a chemical or physical change in living tissues that would resist tuberculous phthisis, it is possible that inoculations with the bacillus would have to be made; yet before this could be done the power of the virulent bacilli would have to be diminished, otherwise the result would be most disastrous."

I considered it possible that the unrecognized forms shown in the cut might perhaps represent the condition of bacilli necessary to prove the truth of the second hypothesis, particularly as animals inoculated with these organisms have survived subsequent inoculations with virulent tubercle bacilli.

This was, so far as I know, the first note proclaiming that an active campaign had been opened on the tubercle bacillus, and specifying in terms of considerable definiteness the means whereby the war was to be carried into the enemy's country.

Later in the same year (1889) I delivered an address before the New Jersey Sanitary Association on the general subject of "tuberculosis," in which I stated that guinea pigs inoculated with this attenuated virus would "resist the action of virulent virus for months at least."

Professor Koch announced in August, 1890, that he had succeeded in developing a substance which had the power of preventing the growth of the tubercle bacillus in man. At that time, however, no hint was given of the method of preparation of the new substance.

On September 6th of the same year an article from my pen appeared in the *Medical and Surgical Reporter* of Philadelphia, in which, referring to my first announcement, I said:

"It will probably be interesting to the scientific world to know that the results published last October have been corroborated by a series of inoculations of the prepared virus into guinea pigs, rabbits, and opossums, after which they have resisted matter so virulent that all animals not previously inoculated with the changed virus took on tuberculosis when inoculated with such matter."

On November 15th, 1890, I announced through the *Philadelphia Times and Register* "That, following out the hypotheses advanced in my terse article in the *Medical News* of October, 1889, had given the most brilliant results."

Three days later I took occasion to lay before the Academy of Natural Sciences of Philadelphia a report summarizing more in detail my work of investigation on the tubercle bacillus in the bacteriological laboratory of the Academy, and stating that animals treated with the involution form of tubercle bacilli continued to resist injections of virulent bacilli.

Realizing the danger of introducing live tubercle bacilli into the human economy, I was with many others laboring to obtain the active principle that would produce immunity. To accomplish this, I submitted the tubes containing tuberculous bacillary growths to the action of ether, and also of a saturated solution of chloride of sodium. The mixtures were then passed through a Pasteur filter

without pressure. This active principle, when subcutaneously injected into tuberculous animals, caused a febrile reaction. The tissue in the immediate neighborhood of the tubercles became hyperaemic, and the symptoms manifested resembled those produced by the introduction of the original mass. This was published in the *Medical News* of Philadelphia, January 17th, 1891.

On May 15th of the same year I had the honor of delivering the annual address before the State Board of Health of Pennsylvania, on the occasion of the Fifth State Sanitary Convention, and selected for my special theme, "Tuberculosis, Its Causes and Effects, Its Treatment and Prevention." In this address I touched upon the question of the relationship between the bovine and the human bacillus of tubercle, and expressed myself as follows:

"Scientifically it will be of particular interest to have the bovine and human tubercle bacillus differentiated, yet for all sanitary purposes we will have to consider the tubercle bacillus of the cow accompanied with it nidus as being destructive to human life; for it is well established that the bacillus of man will produce in the lower animal economy—such as the cow, dog, guinea pig, opossum, etc.—the deadly malady, and that the bacillus of the cow will also bring about a like disturbance in the same line of animals; and, further, bacilli from the rabbit, etc., will in turn reproduce tuberculosis in the cow."

The bovine tubercle bacilli are much more virulent in the lower animals than those of human origin.

In a paper entitled "Possible Relationship Between the Tuberculous Diathesis and Nitrogenous Metabolism," read before the Academy of Natural Sciences of Philadelphia, November 26th, 1894, I called attention to the antagonism of nitrogenous products of the tubercle bacillus, and to its propagation in the tissues of human beings. The idea that those who suffer from gout rarely develop tuberculosis is an old one, and apparently not without substantial foundation. Hence I argued that, as in gout the tissues are overcharged with metabolic nitrogenous products, the direct introduction of such matter prepared in the laboratory of Nature might bring about a condition in the tissues of those suffering from tuberculosis

which would render them resistant to the tuberculous process. I was able to announce successful results in a few cases of lupus vulgaris by the use of taurin, creatin, urea, uric acid, and similar products, and at the same time called attention to a vegetable product very similar to urea named thiosinamin, which had just come into use abroad as a therapeutic agent for tuberculosis.

I further called attention to the possibility of establishing a lithemic habit involving excessive assimilation and metabolism of proteid substances together with increased oxygenation, in order to antagonize or substitute a tuberculous diathesis involving deficient assimilation and decreased oxygenation.

One of the most important events in the history of the campaign against tuberculosis in America in recent years has been the inauguration in Philadelphia of that magnificent foundation, the Henry Phipps Institute for the Study, Treatment, and Prevention of Tuberculosis, of which Dr. Lawrence F. Flick, the Medical Director, has just issued the annual report for the second year, ending February 1st, 1905. The careful analysis of the conditions, sociological as well as medical, of the 1,561 patients treated is worthy of study. A number of valuable reports and monographs, prepared by members of the medical staff, are therein published. One of these is by Dr. Leonard Pearson, State Veterinarian of Pennsylvania, who is also veterinary surgeon of the institute, and is entitled, "A Review of Recent Investigations and Observations Upon the Immunization of Animals against Tuberculosis."

Referring to the tuberculin of Koch, he said:

"It was at last established that while tuberculin has a specific effect upon the lesions of tuberculosis, and in some cases causes the lesion to become encapsulated, to recede, or to disappear, this effect is by no means constant, and is not sufficiently frequent to make this mode of treatment of practical value.

"Some modified tuberculins have been produced by Koch, E. Klebs, von Ruch, von Behring, Buchner, Hirschfelder, Maragliano, and others, but none of them has been sufficient to render an animal immune to tuberculosis permanently or to a practical degree."

The investigations of Stroebe, Arloing, Courmont, Nicolas, Spengler, Hahn, Baumgarten, Maragliano, Babes and Broca, Ferran, Niemann, McFarland, Petterson, von Behring, Dixon, Grancher, Ledoux-Lebard, Hericourt and Richot, Trudeau, McFadyean, and Schlegel are all referred to, more or less in detail. He then goes on to say that "Progress in this line did not occur until efforts were made to immunize animals against living tubercle bacilli by the use of living tubercle bacilli by Dixon in 1889," as published in the *Medical News* of October 19th, 1889.

In the *University Medical Bulletin* of April, 1905, Drs. Pearson and Gilliland published an article upon cattle infected with tuberculosis, giving a line of experiments which consisted in treating them by intravenous injections of a suspension of living human tubercle bacilli, the results of which went to prove a marked curative power of such treatment in young growing animals.

Dr. H. P. Ravenel's report after a visit to Maragliano's laboratory is to the effect that from a laboratory standpoint the experimenter has succeeded in producing a serum which protects experimental animals against the poisons of the tubercle bacillus. The curative value of this serum is not so well established. This latter view is supported by clinical reports on this subject presented by three members of the medical staff of the institute—Drs. Joseph Walsh, William H. Stanton, and H. R. Landis. Five cases were placed under treatment. As compared with other cases under observation at the same times, the results could not be said to be in favor of the serum treatment.

Dr. Ravenel refers to the fact that in the autumn of 1903 Dr. Alexander Marmorek, at that time connected with the Pasteur Institute in Paris, announced that he had produced a serum which was vaccinal and curative.

"The true toxin," he holds, "is formed by very young, or what he terms primitive, bacilli." This may be so, yet my work has demonstrated that the toxin is also produced by old or involuted or degenerated bacilli: therefore, if we fail to obtain a prophylactic serum and

have to continue the use of the bacilli themselves to produce immunity, the involution form will be preferable to the young, vigorous micro-organisms, as there will be less danger of their reproducing themselves and overcoming the animal economy before they produce immunity.

As stated in his "Investigations on the Experimental Illness Caused by the Inoculation of Degreased Tubercle Bacilli,"¹ Cantacuzene, experimenting on guinea pigs, only used dead bacilli of bovine origin, as they prove more fatal than those of human origin. The bacillary bodies were isolated from their environment and completely cleansed and degreased. This was accomplished by paper filtration and prolonged washing in normal salt solution, drying in a vacuum, and then submitting to the successive action of methyl-alcohol and benzine in a Soxhlet apparatus in continuous circulation.

The general symptoms and cellular reactions after the inoculations both of fatal and non-fatal doses were most carefully noted both macroscopically and microscopically in the various organs, tissues, and fluids, including the blood.

Additional experiments were made by submitting the degreased bodies to the action of Gram's iodo-ioduretted solution before inoculation.

His conclusions in brief are:

1. Dead tubercle bacilli completely degreased are toxic. A sufficient dose is followed by speedy death.
2. In non-fatal doses the inoculation is followed by an illness from which the animal recovers completely in about three months.
3. The inoculated animal reacts typically to tuberculin for several weeks.
4. Degreased bodies of tubercle bacilli treated by Gram's solution lose their toxicity.
5. We can hasten enormously the resorption of the degreased bodies and of the tuberculous neo-formations by daily injections of

¹*Annales de l'Institut Pasteur* of Paris for November 21st, 1905.

iodide of potassium, which stimulate to a high degree the phagocytic properties of the mononuclear leucocytes.

This brief review of the work done during the last seventeen years in search of a cure for and a prophylactic against tuberculosis demonstrates that immunity can be produced in the lower animals at least; yet so far our profession stands in this field of research about where it did at the beginning of that period.

We have not been wholly successful with our extracts, but with the bacilli themselves a higher degree of immunity has been attained. For this reason I have taken the liberty on this great occasion to sum up the results accomplished in order to fix upon the minds of us all just where we stand, and to plead with you that we may unite with renewed energy in the search for the active principle, so that we may venture to use it upon the human economy without incurring the danger that must attend the introduction of the bacilli themselves in our present state of knowledge.

The Commonwealth of Pennsylvania, covering a domain of 45,000 square miles, and maintaining a population of seven millions of people, has recently passed a great health law, which confers upon the Commissioner of Health both the funds and the authority to pursue original investigations in search of a means to combat tuberculosis.

I have, therefore, been working to obtain that substance which we know produces immunity to this disease in cattle, and yet while nothing has been obtained which will warrant results being given to the world I am tempted, because of this occasion, to suggest the line of thought upon which my new work is being executed, hoping to tempt my co-workers to help me follow out investigations to either a positive or negative conclusion.

The results of postmortems and the vaccination of cattle with tubercle bacilli have taught us that there is not only something curative, but also preventive. Tuberculin is not an antitoxin. It is a diagnostic agent, and stimulates an incapsulation of tubercle foci, and also causes a special degree of febrile reaction in tuberculous animals.

Therefore, I am injecting cows, in the tissue of the neck, with twenty cubic centimeters of concentrated tuberculin with the idea of producing a re-action, and while the temperature is rapidly rising, drawing the blood and separating the serum which is tested for its active principle by being introduced into both healthy and tuberculous animals, the re-action being carefully noted. The normal serum, of course, is also being injected into check animals.

Upon second thought I appreciated the fact that we have immunity more marked in some parts of the body than in others, which suggests the possibility of the latter containing an antitoxin, yet so far we have failed, as I have said, to get an antitoxin of sufficient potency to be curative. This failure is likely due to the fact that in the first place, if it is produced by the tubercle bacillus, we have not used the right solvent. It has occurred to me, therefore, that it might be possible to obtain the antitoxin by the use of fluids from the animal (but more certainly if we take the serum from those parts of the body which are more naturally immune, like the pancreas). If this protective substance, on the contrary, is produced by the animal cells, would it not be best in making our anti-tuberculous serum to take the blood, not from the general economy, but from parts of the animal which show the greatest tendency to immunity; therefore, from the pancreatic vein.

Again, I am trying a line of experiments by intercepting the blood in the portal system, and using solvents to extract any antitoxin that it may contain before it is acted upon by the liver.

This is an intimation of the line of work now being conducted in the very newly created laboratories of the Commonwealth of Pennsylvania, too new, however, and the time allotted me by this Association too short to venture to give any further details upon this occasion. The results of the work, however, will be published by the State Government from time to time. Should these results be successful, I shall be content, in view of the great good which will accrue to humanity, regardless of credit to myself.

