THE PROBLEM OF IMMUNITY IN TUBERCULOSIS.[1]

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It is my purpose to take a brief retrospect of past achievements in attempts artificially to protect against tuberculosis, and then to indicate what seems to me the special problems for the future. It must be confessed that much discouragement has resulted from the numerous experiments on animals in this direction during the past two decades. This problem has engaged the thought and labor of the foremost workers in immunity research, and it will continue to do so with the enthusiastic hope inspired by every new discovery, however little it may contribute to the ultimate object.

A review of the achievements already attained, with due credit to the authors for priority, is peculiarly difficult, and also impossible in the limits of this address. The difficulties are real because of the simultaneous experimentation in different laboratories and countries, which have independently followed similar lines impelled by the same ideas. The most important example of this common *motif* is the principle of immunization with bacteria of attenuated virulence, formulated by the immortal Pasteur and applied to tuberculosis as soon as the illustrious Koch made it possible by the discovery of the bacillus. It is noteworthy that this principle holds at present the leading place in the hope for success in the future, and it is natural that these experiments should have begun in France (Daremberg, Grancher and Ledoux-Lebard, Martin, Hericourt and Richet, and Courmont and Dor). The immediate results were discouraging; too little was known of the mechanism of immunity to make use of the crude methods then employed as a basis for thorough experimentation; and the discovery of tuberculin and antitoxins for other diseases directed attention to these fields of greater promise.

As it is not generally known that Americans engaged in the earlier experimentation with a considerable degree of success, it is appropriate that they should receive mention here. As early as 1889 Dixon made some preliminary experiments with attenuated bacilli, and Trudeau, working under exceptionally difficult conditions, produced a relatively strong immunity with cultures of avian tubercle bacilli (1892), and later with attenuated human cultures. The late Emil de Schweinitz, in 1894, had more marked success on guinea-pigs immunized with the same attenuated cultures employed in Trudeau's experiments. This period was also one of diligent but unsuccessful search for antitoxic immunity by means of divers extracts and products of the tubercle bacillus. The soluble extracts of tubercle bacilli having failed to immunize

[1] Read at the International Congress on Tuberculosis, Washington, D. C., October 1, 1908.

animals, Koch introduced the emulsions or new tuberculins, "T. R." and "B. E.," which were in some degree protective against infection.

Experiments with pseudotubercle bacilli and mammalian types, supposedly altered by passage through reptilians, also promised fruitful results, but they have not fulfilled this hope up to the present time.

The discovery by Theobald Smith, in 1895, of differences in form and virulence between bacilli from bovine and human sources, was another valuable contribution destined to influence the course of immunity experimentation on cattle. Pearson and Gilliland in America were among the first to attain a high degree of immunity in cattle by the use of the human type of bacilli, following up their first work by an extensive series of practical tests.

During the past decade many workers have turned to the study of immunity against tuberculosis in cattle. Von Behring and Koch with their associates have introduced methods of immunization for cattle, the basis of which was the intravenous inoculation of living human cultures. The "bovovaccin" of von Behring consisted of dried human cultures designed to be twice inoculated within an interval of three months. The "tauruman" of Koch and Schütz was an emulsion of more virulent human type for a single protective inoculation. Coincidently, Pearson and Gilliland succeeded equally well with successive inoculations during shorter intervals. Besides these methods von Baumgarten employed subcutaneous inoculations with good results, Calmette and Guèrin used the gastro-intestinal route by feeding the protective virus, and Heymanns enclosed virulent bacilli in capsules which were introduced subcutaneously for immunization without resulting danger of infection. Klimmer, of Dresden, claims excellent results from the subcutaneous injection of a virulent and modified human bacilli supposed to be passed through lizards.

The world-wide interest created by von Behring's announcement, in 1902, of a practicable method of immunizing calves, led to the hope that this aspect of the problem had been solved. An enduring immunity for cattle with no danger associated with it was an alluring prospect, and extensive experiments were at once undertaken. The outcome of these has been less satisfactory than was hoped for. A high degree of resistance can be conferred by various methods of inoculation with human and attenuated bovine bacilli for a period varying from six months to two years. Unfortunately, exposure to natural infection or to inoculation with bovine virus after this period has resulted disastrously. Some of the animals completely lose their immunity and others retain but little of it. The situation is, therefore, at present not encouraging for the establishment of a long-continued immunity by any method, either in cattle or men.

Moreover, the use of living virulent bacilli as a bovine vaccine, either intravenously or subcutaneously, cannot be regarded as safe,

since they have been discovered in the subcutaneous abscesses and milk at least nineteen months after the protective inoculation (Schroeder and Cotton, and Weber and Titze). The trend of experimentation has naturally been toward the use of bacilli either deprived of reproductive power or modified by conditions of growth so as to lose parasitic features. The possibility of a strong relative immunity has been demonstrated, but much yet remains to be accomplished to make it useful.

To overcome the objections due to the use of living human bacilli in cattle, and to apply the principle of immunization to mankind, have been the problems of recent years. Hope of this achievement was held out by von Behring at the last International Congress at Paris in 1905. Nothing definite has been made public since to indicate that this hope was justified or that the immunizing and therapeutic properties of the so-called "tulase" were superior to the bacillary preparation T. R. of Koch, introduced a decade before.

One fact has been prominent in the course of all investigations, and that is the superiority of living bacilli over all the preparations of dead bacilli for protective inoculation. The vital element has a more pronounced influence, even upon animals which completely resist infection by the immunizing vaccine and show no trace of the inoculated bacilli a short time afterward in their tissues. It is natural to suppose that the bacilli perish too quickly to adjust themselves to a parasitic existence by producing any hypothetical secretion, which might be the secret of their greater protective influence. It is admitted, however, that the degree of immunity is directly proportional to the virulence of the vaccine. The subtle difference between the immunizing value of living and of dead bacilli needs more investigation; likewise also the cause of variations in virulence.

Repeated protective treatment must be considered necessary for success from the present outlook, and by means of an agent equally innocuous to cattle and mankind. It has been found that a period of two months after the first immunizing dose is required to develop the specific resistance in calves. Obviously, they must be protected from exposure to infection during this period. Probably the subsequent protective treatments will more quickly become effective.

It appears desirable to establish as strong local resistance as possible by subjecting all avenues of infection to local immunization; for example, by feeding and inhalation of the vaccine.

In order to adjust the dosage and intervals the finer mechanism of immunity must be closely studied. The agglutinin and opsonin tests have not been satisfactory measures of resistance, and some way of estimating specific latent antituberculous cell energy is needed. When natural infection is taking place or the individual is undergoing immunization there are, it is true, evidences of

changes in the blood, but when no such stimulus is active the content of antibodies—agglutinin, opsonin, or lysin—slowly drops to a normal level. There is then no sign of the latent specificity which we are as yet able to recognize, although a renewed infection or a tuberculin test may elicit it.

Another phase of the problem is to establish a correct balance between the specific response to infection, which occurs during the hypersensitive stage of immunity and the ability of the tissue cells to assimilate the poisons without harm.

An immunity that tends only to arrest the infection but not to overcome it, is not wholly beneficial when it creates ulceration at the portal of entrance of the bacillus (Th. Smith). Hence the question whether hypersensitiveness artificially induced by protective inoculations is beneficent or otherwise must be considered. It would seem vastly better, from what we know of the effects of hypersensitiveness in heightening the affinity of the body cells to a harmful degree for the poisons of tubercle bacilli, that it should be avoided. Specific bacteriolytic powers are useful in combating bacteria, but not in assimilating the dead and digested body substances of bacteria.

Fortunately the number of bacilli to be disposed of at any given time is small under natural conditions of infection. It is conceivable that a relative tuberculosis immunity without tuberculin susceptibility being produced at some time during its development might be defective. On the other hand, complete tolerance to tuberculin in cattle may be associated with a high degree of resistance to infection.

The problem, therefore, seems to be to create tolerance for the bacillus poisons and its products which have resulted from lysis, or to aid their safe assimilation by the tissues.

Without the unknown quality called "tolerance" no real immunity can exist, and the earlier in life this can be established with absolute safety the more resistant the adult must become. That there is danger of harm in the process may easily be surmised from the grave impairment of nutrition resulting from experiments with dead bacilli, and the well-known anemia accompanying so-called latent tuberculosis. These difficulties I conceive to be the prominent ones, but they are here treated in a confessedly superficial manner.

The studies of Bartel on the influence of lymphatic cells upon the tubercle bacillus, as well as those of Opie on the leukocytes, promise to enlarge our knowledge of this subject. Still more light may come from investigations now in progress on the mechanism of anaphylaxis and its prevention.

Finally the problem of passive immunity is still a distant goal which should not be forgotten. It must not be thought hopeless considering the progress of biologic research, though a serum therapy furnishes but a faint probability of success. Some other method of

directly neutralizing the cell poisons may yet be discovered with the increasing facilities generously being devoted to medical research. On this rests the hope of an efficient therapy to supplement all other means of prevention and cure.

THE CAMMIDGE REACTION IN EXPERIMENTAL PANCREATITIS.[1]

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IT is rather surprising that, despite the great clinical value claimed for his test, Cammidge[2] has so far made no attempt to control his observations by experimental work. Eichler[3] studied the effect of experimental pancreatitis on the urine, producing in one dog hemorrhagic pancreatitis, and in two dogs a diffuse purulent pancreatitis. The urines of these dogs before operation were negative, confirming the observation previously made that the urine of normal men, dogs, and rabbits does not give a positive pancreatic reaction. The post-operative examination of the urine, in each instance, was positive, which led Eichler to conclude that the test is of great value in diagnosticating pancreatic disease. As he used the *A* and *B* reactions in his studies, and as these reactions have been severely criticised by Ham and Cleland,[4] Schroeder,[5] Gruner,[6] Wilcox,[7] and Haldane,[8] the the value of Eichler's conclusions may be questioned.

In 1907 Cammidge[9] described a third, or *C* reaction, which he claimed does away with many objections raised by his critics. Very little clinical work has been done with the *C* test, apart from Cammidge's own researches, and, so far, no experimental work has been reported. The papers of Cammidge, Schroeder,[10] and Goodman[11] have presented so much clinical evidence in favor of the reactions that we deemed it advisable to control these observations by experimentation.

[1] Read at a meeting of the College of Physicians of Philadelphia, December 2, 1908.
[2] Robson and Cammidge, The Pancreas: Its Surgery and Pathology, 1908.
[3] Berl. klin. Woch., 1907, p. 769.
[4] Australasian Medical Gazette, 1904, p. 399; Lancet, 1904, i, 1378.
[5] Amer. Med., 1904, p. 406.
[6] Lancet, 1904, i, 1459.
[7] Lancet, 1904, ii, 211.
[8] Edin. Med. Jour., 1906, xx, 418.
[9] Loc. cit., p. 252.
[10] Jour. Amer. Med. Assoc., 1908, li, 837.
[11] Read by invitation at a meeting of the Philadelphia Academy of Surgery, November 2, 1908, and to be published in the Annals of Surgery, February, 1909.