SCIENCE

VOL. LVII APRIL 27, 1923 No. 1478

SCIENCE: A Weekly Journal devoted to the Advancement of Science, publishing the official notices and proceedings of the American Association for the Advancement of Science, edited by J. McKeen Cattell and published every Friday by

THE SCIENCE PRESS

100 Liberty St., Utica, N. Y. Garrison, N. Y.
New York City: Grand Central Terminal

Annual Subscription, $6.00. **Single Copies, 15 Cts.**

Entered as second-class matter January 21, 1922, at the Post Office at Utica, N. Y., Under the Act of March 3, 1879.

THE METHODS OF IMMUNOLOGY[1]

DURING recent years your president has been denied the opportunity of continuing research work, by reason of constantly increasing administrative responsibility. Any one of you who has had similar experience will understand the sacrifice involved in being divorced from immediate participation in investigations. For the reason stated I am unable to present to you any piece of research, but in lieu of this I shall venture to tell you briefly of the great aid afforded by your own particular branch of biological science to those of us who are confronted with the responsibility for the final supervision of certain medicinal agents.

It is a fact that governments (and particularly our own) have singled out from the great list of remedial and prophylactic preparations those susceptible of examination by immunological methods, and have placed in the hands of certain agencies control procedures applicable to those agents and unthought of in connection with other groups of therapeutic preparations. Let me make this clear by an example:

At present no one may exploit in interstate traffic in the United States serums or vaccines for the treatment of cancer, but there is nothing to prevent any one from exploiting a treatment for cancer made of something other than a serum or vaccine, provided only that the labels on the preparation conform to the requirements of the food and drug enforcement officials.

In our country Congress in 1902 recognized the importance of, and the special dangers and needs in connection with, biologic products, and in the intervening period the hygienic laboratory of the United States Public Health Service has had exceptionally good opportunities of becoming familiar with the difficulties involved, as the control measures are exercised through that institution.

[1] Presidential address before The American Association of Immunologists, Boston, March 29 and 30, 1923.

I shall now briefly review the procedures in connection with the preparations in which biologic control is exercised.

SERUMS

We naturally consider first the *antitoxins* which have well-recognized potency standards. I shall dismiss diphtheria and tetanus antitoxins by saying that the standards for these are so satisfactory and so well known that the distribution by the central testing laboratory of standard serums for comparison enables producers to titrate their products satisfactorily, and, beyond occasional testing of market samples for comparison of results with those secured by manufacturers, no further measures are necessary.

It is less well known that there has been established a standard for botulinus antitoxin of types A and B, and a standard for the antitoxin against gas gangrene—*B. Welchii* or *B. perfringens*. In the case of these products, however, it is customary for manufacturers to control all of their own tests by forwarding samples to the central testing laboratory for the making of comparative determinations. We are indebted to Miss I. A. Bengston for the standard in the case of each of these anaerobes.

Finally, under this head it may be stated that we are endeavoring to establish an antitoxic unit for antidysenteric serum, but thus far the work has scarcely gone beyond the place where we can say that the serum has or has not antitoxic value. Perhaps if bacillary dysentery of the Shiga type were a more serious problem in the United States we might make better progress in this line.

Antibacterial serums: The most important of these is antimeningococcic serum, and it has occupied a large part of our time during the past five or six years. Starting with the simple agglutination test against the various types of meningococci we have gradually extended the work until at present, in addition to this, we often employ the complement fixation test, and even more often the determination of the bacterio-tropins; tests for the latter in this particular connection have been placed on a workable basis by Miss Alice Evans. The protection tests, devised by Gordon a few years ago, were given a fair trial but discontinued as we were unable to get such consistent results as Dr. Gordon seemed to have been able to secure. Indeed, in this case it is not at all clear that protection tests would be of more value than the tests we now employ, since it is possible that the mechanism of protection in animals might be entirely different from the mechanism of therapeutic action in the spinal canal, as the serum is ordinarily employed. Full recognition is of course given to the various types of the organism in all of our tests.

Antipneumococcic serum has been tested at an expense of time and money perhaps unwarranted by the practical utility of the preparation. A mouse protection test, modified from the one originally employed by Neufeld and later extensively used by the workers at the Rockefeller Institute, is in constant use and unquestionably gives a fair degree of evidence on which to judge of the value of the preparation, so far as can be determined by animal tests.

Antistreptococcic serum: In connection with this we have to record only failure to accomplish anything beyond tests which show streptococci have been employed in immunization of horses, and that the resulting serum is protective against small doses of the homologous organism.

It is an interesting fact that this serum, which is on such an unsatisfactory basis from a scientific point of view, is very extensively employed by clinicians, perhaps more extensively than any of the other antibacterial serums.

Antianthrax serum: This serum is not extensively employed in human medicine, but it has occupied the efforts of several of our workers and we are hopeful that satisfactory protection tests may be adopted in the near future. Our work so far has clearly shown the futility of strictly test-tube immunological examinations.

BACTERIAL VACCINES

In connection with this group of rather extensively used preparations, we are again confronted with the question as to whether the value of the preparations is such as to warrant the time and money spent on the efforts at standardization, beyond those necessary to establish tests to assure the safety of the product, since time and money are not available adequately to control all preparations coming under the law and regulations.

Another question, which may fairly be raised

in connection with preparations falling into this as well as into some other groups, is whether or not it is possible that the standardization of preparations of dubious prophylactic and therapeutic activity may give rise to a fictitious and wholly unwarranted confidence in the preparations. An exception must be made to this generalization, and this of course is with reference to antityphoid vaccine, the proven worth of which has made it necessary to adopt a standard test on its agglutinogenic qualities, a criterion which we realize is not satisfactory, although it is the best we have.

TOXINS AND SIMILAR PREPARATIONS

We consider here diphtheria toxin for the Schick test. Standardization is based on the Minimal Lethal Dose, and to meet the common practice of the day provides for dosages of one fiftieth and one fortieth of the guinea pig minimal lethal dose as the human dose.

Toxin-antitoxin mixture: The mixture is tested for toxicity, both as to its ability to cause death to the test animals within the usual period of four days and its ability to produce paralysis and later death.

POLLEN EXTRACTS

Pollen extracts are on a most unsatisfactory basis and we are now working on serological tests, controlled by clinical observation, in the hope that one may be adopted or developed which may serve as an index to the desensitizing value of the preparation.

TUBERCULIN

This is still another of the preparations which have occupied more of our time and thought than is warranted by their importance from a therapeutic or prophylactic point of view. We are unable to report any successful outcome of the work which has been devoted to this preparation.

VIRUSES

The most important of these is smallpox vaccine, and there is now actually in use at the hygienic laboratory a method (not original with us) which, by the inoculation of rabbits with a series of dilutions of commercial vaccine, enables us to form a rough estimate of the potency of the material. This particular preparation is so susceptible to external influences, particularly to the temperature at which it is kept, that a potency test satisfactory to-day gives no indication whatever of the efficiency of the material a few days later, if it has been kept under conditions unfavorable to the preservation of the virus.

ANTIRABIC VIRUS

The several modifications of the classical Pasteur treatment, which itself is still in use, have all been examined sufficiently to lead us to believe that the various preparations will, when properly used, serve to prevent the development of rabies when applied sufficiently early.

From this hasty survey you will see that the immunological art is very extensively applied in the control of biologic products and that there are ample fields of investigation in this line which, when sufficiently worked, will enable us to place all of the preparations which are of value on a sounder basis than we have for many of them at the present time.

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SOME MODERN PROBLEMS IN LEATHER CHEMISTRY[1,2]

WHEN the literature of leather chemistry of twenty-five years ago is compared with the publications of to-day, one is impressed by the extraordinary progress that has been made in a quarter of a century. The striking feature of the newer papers lies not so much in the results of technical and practical use, although such are to be noted, but first and foremost in the entirely different point of view in the choice and treatment of the problems. The pioneers in leather chemistry, among whom I would especially mention W. Eitner in this connection, have collectively produced a lot of valuable experimental data which they worked up solely from the standpoint of direct practical application. They have opened up an exceedingly fruitful field of experimentation, also quite naturally utilizing contemporary

[1] Translated from German by A. W. Thomas.

[2] Presented before the Leather Division at the sixty-fourth meeting of the American Chemical Society, Pittsburgh, Pennsylvania, September 4 to 9, 1922.