capable also of provoking inflammation. He ascribed separate effects to their paralysis and to their stimulation, and brought an array of experimental and clinical evidence into support of his views. His experiments though numerous were crude, and possess little value to-day. On the clinical side he cited many previous reports, and followed Brown-Séquard's view (1859) that herpetic eruptions after nerve injuries are irritative and Baerunsprung's attribution of zoster to affection of the spinal ganglia. Tangible evidence for the existence of a distinct system of nerves having the functions he ascribed to them is not to be discovered in his book, and his hypothesis rightly won little credence; there has been no reason to believe that nerves influence the nutrition or growth of tissue directly, but only indirectly by altering blood flow or by controlling the tissue's specific function. But although Samuel's hypothesis failed he was right in stressing as unexplained the apparent effects of nerve irritation. The mystery of the cases that have come to be called "causalgia" has remained; when Brown-Séquard concluded such lesions to be the result of irritation he may have been correct, but this fails to satisfy. Samuel's suggestion that they result from the excessive action of his special nerves of nutrition, an overaction exploding in inflammation, was not grounded on proper evidence; but it contained an element of truth. For according to our present evidence distal stimulation of cutaneous nerves does provoke some of the phenomena of inflammation—namely, hyperalgesia and reddening—and may conceivably provoke more. And it is of further interest to remark that while we cannot follow Samuel in regarding the nerves involved as special nerves of nutrition, we are coming to regard them as nerves exercising a special function, termed for convenience "nocifensor."

Conclusion

We have concluded that a specific system of nerves, connecting to at least the skin, exists. This system of nerves is capable of effecting changes in the skin locally and without reference to the central nervous system, though very possibly also capable of excitation from brain or cord. In speculating about the mode of action of these nocifensor nerves with a view to presenting a fuller if more hypothetical conception of them we might venture to suppose that they are nerves exercising no direct influence upon the nutrition of the skin but comprising in their actions an influence more akin to a process of secretion—and in parenthesis it is interesting to note that Charcot inclined to interpret Samuel's ideas in a similar sense. We might regard the nerves as liberating potent substances from cellular elements of the skin into surrounding spaces, and thus controlling partly or wholly within the skin important elements of defence, including inflammation.

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ACTIVE IMMUNIZATION AGAINST TETANUS

BY

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Passive immunization against tetanus was used with considerable success during the great war. In October, 1914, there were thirty-two cases of tetanus per 1,000 of the wounded admitted to the hospitals in England, but in November, after the general adoption of passive immunization of the wounded, the incidence fell to 1.7 per 1,000, and among those cases which did occur the mortality was lower.

Objections to Passive Immunization

Passive immunization, however, has serious disadvantages. Antitoxin, to produce the best effect, should be injected within twenty-four hours of sustaining the injury; this, for several reasons, may in many cases be impracticable. Another disadvantage is that antitoxin from the introduction of a foreign serum quickly begins to disappear from the circulation, and within a fortnight is no longer in sufficient concentration to afford protection; the injection has to be repeated at weekly intervals and before any subsequent operation is undertaken, since tetanus bacilli or spores may remain latent in the tissues for a long time.

Another serious drawback is the sensitization to horse serum, which to a greater or less degree follows immunization with antitoxin derived from immunized horses, a sensitization continuing for many years. Troublesome serum reactions, and even severe and in some cases fatal anaphylactic shock, may accompany or follow the subsequent injection of a therapeutic serum which may be urgently required in the treatment of an infection such as diphtheria.

Sensitization also considerably diminishes the immunizing effect of a further injection of serum. Glenn and Hopkins (1922) found that while in the case of a normal rabbit the titre of antitoxin in the blood dropped to a low level in twelve days after the intravenous injection of antitoxic horse serum, in the case of a rabbit sensitized to horse serum the same low level was reached in four days. Kahn and McDermott (1934) found that while the injection of 5 units of diphtheria antitoxin could protect a normal rabbit against fifty minimum lethal doses of diphtheria toxin, 75 units were required when the animal was sensitized to horse serum.

Tetanus Toxoid

Active immunization by tetanus toxoid has none of these disadvantages. There is no more difficulty in immunizing against tetanus than against diphtheria; it is quite free from danger and the result is just as satisfactory. Complete and permanent immunity is obtainable. A commission to study the question of prophylaxis against tetanus in the French Army strongly recom-

mended the adoption of wholesale immunization with toxoid in the place of passive immunization with antitoxin, which latter should be reserved for any of the wounded who might not have been actively immunized, and even in that case only as a preliminary stage in active immunization.

Ramon and Zoeller (1927) immunized several hundred persons by three injections of toxoid given in the same way as diphtheria toxoid. The antitoxic content of their serum subsequently averaged from 0.3 to 1 unit per c.cm. After four years the titre had dropped considerably—to from 1/500 to 1/6 unit per c.cm.—but the injection of another dose of toxoid raised the antitoxic content of their blood to 3 units per c.cm. After the injection of 1,700 units of antitoxic serum the antitoxic titre of the blood does not reach more than 0.17 unit per c.cm., and that for a few days only.

P. A. T. Sneath and E. J. Kerslake (1935) in Toronto estimated the antitoxic content of the blood in persons who had been immunized by the subcutaneous injection of three doses of tetanus toxoid. Thirteen of them were examined two years after the immunization. The titre of antitoxin remained at much the same level as it had been twelve months previously; in three of these there was 0.1 unit per c.cm. Another injection of toxoid was then given, and within a week in eleven out of the twelve the titre had risen to amounts between 1 and 10 units per c.cm.—from ten to five hundred times the former level. One person responded poorly to immunization, and in this case the titre did not rise above 0.025 unit. Horses differ greatly in their response to immunization, and it is not surprising that human beings differ in the same way. The efficiency of the antibody producing activity of the reticulo-endothelial system, and consequently the response to immunization as indicated by the antitoxic content of the serum, varies greatly in different individuals. In a few cases it has been found difficult to immunize sufficiently with diphtheria toxoid to produce a Schick-negative reaction, and Schick himself said he believes that "there are some individuals who are totally incapable of developing antibodies against diphtheria." Fortunately such instances must be very rare.

Tetanus Alum-toxoid

Glenny (1930) investigated the immunizing effect of tetanus alum-toxoid on guinea-pigs and horses, using the precipitate formed after the addition of alum to tetanus toxoid. He found that in the hyperimmunization of horses "the addition of alum to tetanus toxoid doubled the value of the antitoxin produced . . . and if horses were rested for a month or more after a primary stimulus before immunization was continued much stronger antitoxin was produced." This principle is adopted by Dr. G. F. Petrie in the immunization of horses at Elstree. An injection of alum-toxoid is given on admission to the stables, a second injection two or three months later, and then the injections are repeated every six months.

D. H. Bergey (1934) also found that alum-toxoid gave better results than untreated toxoid. When 1 c.cm. was injected into a guinea-pig the animal's serum contained 1 unit of antitoxin per c.cm. after ninety days, when a second injection was given; fifteen days later the content of the serum rose to 9 units per c.cm. Bergey used the same preparation of alum-toxoid to immunize thirty-five adult persons whose serum before immunization contained on an average 0.0001 unit of antitoxin per c.cm. Ninety days after the first inoculation the titre had risen to between 0.001 and 0.04 unit per c.cm., but a second injection 125 days later raised the antitoxin content to

from 0.1 to 9 units per c.cm.—an increase of from one thousand to nine thousand times the original amount.

Alum-toxoid was prepared by adding alum (1 per cent. or rather less) to the toxoid solution. The resulting precipitate before being used for inoculation was thoroughly washed to remove any traces of alum or protein from the culture medium in order to avoid skin reactions. None of the inoculated persons complained of local or general reactions.

Conclusion

There seems to be no doubt that by the injection of toxoid or of alum-toxoid, which seems to give even better results, it is possible to confer complete and permanent immunity on the vast majority of those inoculated. The immunity thus produced depends not only upon the presence of antitoxin in their blood but to a still greater extent upon the "sensitization" of the reticulo-endothelial cells to tetanus toxin, and results in a much greater and more active response to the antigenic stimulus, so that infection by tetanus bacilli at any later date will be countered by a rapid and increased output of antitoxin sufficient to afford complete protection.

Such protection might be afforded to the British Army by the injection of two doses of alum-toxoid at an interval of three months, with the additional protection of a third inoculation before being called upon for foreign service or in the event of war. This last inoculation might be combined with anti-typhoid immunization, since it was found by Ramon and Zoeller (1927) that the efficacy of tetanus toxoid in immunization was actually increased if a bacterial vaccine such as T.A.B. was injected at the same time.

The papers referred to in this note are a few only from many that have been written on this subject in recent years.

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A. Weissmann (*Wien. klin. Wschr.*, December 18, 1936, p. 1556) draws attention to the value of hyperthermia in the treatment of myalgia, neuralgia, neuritis, chronic arthritis, neurosyphilis, etc. This is supposed to be due to increase of resistance on the part of the organism, which results in hastening the process of repair. The author has produced hyperthermia therapeutically for the past six years by using a modification of Walinski's pack. The patient is given a bath at 37° C., wrapped in a flannel and six woollen blankets, and left for six to eight hours. Physical and chemical treatment—namely, injection of proteins—combined allow of smaller quantities of the latter to be used. Fever is induced every second day, and in most cases a course of twelve packs suffices. The injection of 10 c.cm. of 20 per cent. salt solution for the prevention of sweating, according to Walinski's original method, is stated by Weissmann to be unnecessary. Hyperthermia should never be produced in tuberculous cases or in those with cardiovascular disease. The author also recommends a pack used by Abrahamowicz, which is milder than Walinski's and more pleasant for the patient. Different varieties of herbs exposed to x rays and ultra-violet light are put into thirty little sacks and heated to 45° C.; fifteen sacks are placed below and fifteen on top of the patient, who is wrapped in a rubber and woollen blanket. In three-quarters of an hour the temperature may reach 39° C. The pharmacological action of the herbs and the setting free of vitamins through radio-activity as declared by Abrahamowicz are denied by Weissmann.