ON THE TREATMENT OF ENTERIC FEVER WITH TYPHOID VACCINE.

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Contents.—Fraenkel has injected beneath the skin of enteric patients, dead typhoid cultures.

Therapeutic inoculations in Rabies, Tubercle, Plague, Micrococcus melitensis, Staphylococcus, Streptococcus, Gonococcus, Pneumococcus, Bacillus coli communis, and Proteus infections.

Daily injection of 10,000,000 dead typhoid bacilli into various parts of the subcutaneous tissue recommended.

In a long-forgotten paper which appeared in 1893, E. Fraenkel[1] reported the results of the treatment of fifty-seven cases of enteric fever with the subcutaneous inoculation of cultures of the typhoid bacillus which had been sterilised by heating to 63° C. The strength of the vaccine was such that when 3 cc. were introduced into the peritoneal sac of a guinea-pig weighing 350 grammes no serious symptoms ensued.

He began by administering ½ cc. to his fever patient, followed by 1 cc. next day. Usually a fall in the temperature was noted after forty-eight hours, and a subsequent range at a lower level than before. If the curve afterwards tended upwards, another injection of 2 cc. was given. This was repeated two days later, should no response have been observed.

Fraenkel satisfied himself that good resulted from this method in the majority of instances, and that the fever was aborted in many. These are his words: "Man schneidet fast ausnahmslos die Fiebris continua ab, es kommt von anfang an zu einem ausgesprochen remittirenden charakter des Fiebers, und es erfolgt in unverhältnissmassig kurz zeit völlige apyrexia."

This contribution attracted little notice in the English medical press, probably because it seemed irrational to treat a fever in which the chief symptoms indicate a poison circulating in the system, with additional doses of the toxic agent. No doubt if we introduce the typhoid toxin directly into the veins the cumulative effect of the poison would be manifest. Fraenkel injected the dead bacteria into the subcutaneous tissues and gluteal muscles. This gives an explanation of an otherwise perplexing phenomenon.
Wassermann and Citron [2] have conducted some very important experiments on the local immunity of different parts of the body. They have proved that living tissues produce protective substances at the site of injection of bacteria. The cells in actual contact with the microbe are they which elaborate the defensive products. Thus they introduced typhoid emulsions into the pleural cavity of rabbits and found that the pleuritic exudation contained more bactericidal elements than the blood or fluids from other serous sacs. Again, they injected typhoid cultures beneath the skin of the ears of rabbits, and estimated from day to day the amount of protective bodies present in the blood. After a time they amputated the inoculated ear of one of the rabbits. A sudden fall in the quantity of anti-bacterial bodies in the blood was the consequence when compared with that of the blood of the other rabbits. This showed that the ear removed had been the nidus where the protective elements were being generated. In short, they found that the products evolved for the defence of the organism are always in greatest amount at the site of the inoculation. This, therefore, was the position: Fraenkel introduced the dead typhoid bacilli into a part where they were rapidly fixed by the tissues. The cells were excited into action and responded immediately by the elaboration of substances inimical to the bacteria. Not only did they produce them in such quantity as to deal effectively with the dose of toxin injected, but their activity did not cease and over-production resulted. This excess of immunising bodies was spent in combating the living bacteria causing the fever. Much evidence is forthcoming, and is accumulating daily, that this is a general principle. We will cite the following examples.

A huge experiment, altogether favourable, on the influence of inoculation during infection, has been going on since 1885. In that year Pasteur commenced his treatment of persons bitten by rabid animals, with emulsions of the spinal cords of rabbits, which had died of rabies artificially induced. Beginning with emulsions of a cord, the virus of which had become attenuated by drying, he injected into the flanks of the patients emulsions of cords of increasing virulence in rapid succession, until finally the victim of the bite received, subcutaneously, virus which, if injected into the anterior chamber of the eye, or beneath the dura-mater of a rabbit, would unfailingly cause rabies and death within ten days. The following figures prove how effective these anti-rabic inoculations have been: Since 1885, 108,000 [3] people have been subjected to this treatment. Their death-rate from hydrophobia has been about
The mortality from rabies of those bitten by mad animals who have received no anti-rabic inoculation, has been variously estimated from 16 to 80 per cent. If we take the lower figure it will be seen there has been a saving of nearly 17,000 lives through the genius of Pasteur.

This affords the most striking example of the efficacy of the injection of a virus in the course of an infection. It may be best explained by supposing a very rapid elaboration of protective substances in the area of injection of the cord emulsion. These bodies compass the destruction of the virus introduced by the rabid animal at the moment of the bite, which is slowly travelling along the nerves to the cerebro-spinal system.

Another great experiment on inoculation in the course of infection is the treatment of tubercular disease with the "new" tuberculin. Rather more than nine years ago Koch [4] brought out this remedy, denoted "T. R.," which is nothing more than an emulsion of washed dead tubercle bacilli. This has been extensively used. Reports on its beneficial action are numerous. Trudeau's[5] observations extend over a long period and deal with 1,367 tubercle cases treated hygienically, and 143 with the addition of tuberculin. He found that there were 20 per cent. more successes in the latter than in the former. He thinks that the administration of tuberculin as an adjunct to sanatorium treatment gives more recoveries and fewer relapses than sanatorium treatment alone, and seems to influence favourably the disappearance of tubercle bacilli from the sputum. Lawrason Brown [6] confirms Trudeau's statistics. Pottinger [7] has treated 589 cases with T. R., or allied substances. He claims that 84.2 per cent. were cured. Of 611 other tubercular patients there were 64 per cent. recoveries only. Healing was more rapid and relapses were less numerous under this specific medication. Denys [8] was successful in benefiting 71 per cent. of 442 patients by tuberculin injections. He holds that a cure may be looked for with confidence if the process has not gone beyond consolidation. His series includes invasions of the pleura, peritoneum, glands, bones, joints and intestines. J. Sawyer [9] has employed T. R. in 25 cases of early phthisis. He noted improvement in all, and is satisfied that it is a curative agent of value. O. Amrein [10] has given it to twenty-four patients with good effect. Kinney [11] has used this specific remedy for seven years, and concludes that there is no treatment comparable with it in effectiveness in uncomplicated tuberculosis. Max Elsaesser [12], from an experience of the administration of T. R. to seventy-six
Treatment of Enteric Fever with Typhoid Vaccine

Phthisical patients, is convinced that under its influence appetite improves, bacilli and stethoscopic signs tend to disappear. Kraus [13] is also eulogistic. He has observed diminution of fever and pulmonary symptoms and amelioration in general under it. Lüdke [14] and Petrusky speak well of the use of tuberculin in various tuberculous conditions.

The employment of tuberculin as a curative agent has been put on a more exact basis by the illuminating researches of Sir A. E. Wright [15]. With his method of opsonic index determination it has become possible to measure the effect of the inoculation, to graduate the dose, and to fix the time of its administration. He has published noteworthy successes in the treatment of tubercle of the skin, glands, bladder, peritoneum, and bones. Bulloch [16], guided by the opsonic index, has announced remarkable instances of recovery or improvement under T. R. in cases which had long resisted other therapeutic measures. Lawson and Stewart, [17] with a large sanatorium experience, and after much painstaking work in making between 2,000 and 3,000 estimations of the opsonic index, conclude that in T. R. we have a valuable agent. With it the resistance and power of combating tubercle can be raised to a higher level than is often obtainable by hygienic treatment. Pardoe, [18] is of opinion that in twenty-one cases of tubercle of the urinary system it was the best remedy at his disposal. Loveday [19], H. M. W. Gray [20], Whitfield [21], Emery [22], Ross [23], Butler Harris [24], Crace-Calvert [25], report numerous cases of tubercle treated with T. R. according to Wright's methods; they also testify to its value.

Inoculations against plague of sterilised cultures of Bacillus pestis have been carried out in India on a very large scale, and it must necessarily have happened that some of the subjects were already infected when vaccinated. Bannerman [26] has collected 225 such instances. Their death-rate from plague was 50 per cent., against a mortality of 74 per cent. among the uninoculated. R. W. Hornabrook [27] has recorded a mortality of 39 per cent. in eleven plague patients inoculated with anti-plague vaccine during the infection. That of the unvaccinated was 77 per cent. Alice Corthorn [28] mentions four recoveries of plague-stricken people whom she had inoculated after they had contracted the disease.

For Malta fever, which has been hitherto a reproach to therapeutics, a hopeful remedy appears to have been discovered in sterilised cultures of the Micrococcus melitensis. S. T. Reid [29] has reported nine recoveries accelerated through injections of the
emulsion, the doses of which were regulated by the opsonic index of the patient. A case in the eighteenth month of disease, under treatment at the Queen Alexandra Hospital, is now receiving these inoculations, with the result that his opsonic index is raised and improvement has begun.

Staphylococcic diseases, such as chronic furunculosis, sycosis, acne, have been greatly benefited by inoculation with staphylococcic vaccine. Wright [30] has recorded thirty successful cases. Stopford Taylor [31], Weinstein [32], and Gray [33] have similarly announced good results. Kenneth W. Goadby [34] has treated eleven cases of long-standing alveolar suppuration, some of which had been undergoing other therapeutic measures for years without avail, with sterilised emulsions of staphylococci. He attained a marked degree of success.

In the more formidable streptococcic invasions, such as malignant endocarditis, cases which have resisted repeated doses of anti-streptococcic serum have yielded to inoculations of sterilised emulsions of the Streptococcus isolated from the patient's blood. Barr [35] records an example.

Coleman [36] relates how he successfully treated a case of lobar pneumonia by injecting beneath the skin sterilised cultures of Fraenkel's pneumoccus. Ross [37] also, has cut short a pneumococcic empyema by the same means.

The sequelae of gonorrhoea have been abated by raising the opsonic power of the blood against the gonococcus by means of subcutaneously administered sterilised emulsions of the gonococcus.

Wright [38] has published cases of invasions of the gall-bladder, ducts, and urinary bladder by the B. coli communis, which had proved intractable to treatment, benefiting greatly by inoculations of sterilised emulsions of the bacillus isolated from the bile or urine in question.

Proteus infection of the bladder has improved under the administration of proteus vaccine. Wright reports an instance.

Löwenstein [39] proposes to treat lepers with heated emulsions of leprous nodules. The same author suggests that sufferers from trachoma should be inoculated with sterilised suspensions of the contents of the granules of the affected eyelids.

It is therefore abundantly evident that subcutaneous injections of the appropriate vaccine in the course of an infection have a therapeutic value. The invading parasite does not harm all the tissues of the body in the same degree. For instance, the virus of
Treatment of Enteric Fever with Typhoid Vaccine

hydrophobia introduced by the bite of the rabid animal manifests a preference for the peripheral nerves along which it travels to the central nervous system. We therefore requisition the services of the cells least influenced by the microbe and by stimulating them to activity with the specific vaccine we cause them to elaborate substances antagonistic to the parasitic foe. The sufferer then manufactures his own anti-bodies instead of our endeavouring to provide them for him ready made in the form of serum derived from an immunised horse—an attempt which too often ends in failure. This production may begin early and proceed quickly. In anti-rabic inoculation protective elements must be evolved with great rapidity. On the sixth day of Pasteur's intensive method, an emulsion of so highly a virulent cord is injected that it would of itself induce rabies in the individual if immunity had not been established by the inoculations on the five preceding days. Wassermann and Citron sometimes observed that substances inimical to the bacteria were present at the site of the inoculation in twenty-four hours. Wright and others have noted a rise in the opsonic index often on the day following the administration of the vaccine. It therefore seems reasonable that therapeutic inoculations should be commenced early and continued daily. But the dose must be small. The infected organism reacts more markedly than the healthy body. The tuberculin and mallein methods of diagnosis of tubercle and glanders in animals are based on this sensitiveness. Wright has reduced his doses of T. R. from the \( \frac{1}{2} \) mgr. originally recommended by Koch, to \( \frac{1}{4} \) mgr. in some cases. All observers are unanimous in emphasising the necessity of the use of extremely small quantities of this agent. W. S. Harrison [40] states that 1 cc. of the anti-typhoid vaccine prepared at the Royal Army Medical College contains 500,000,000 bacteria. This is the dose authorised for the first preventive vaccination. The reaction which arises therefrom is not severe. All symptoms have disappeared as a rule in thirty hours. It is suggested that \( \frac{1}{5} \) cc., or 10,000,000 typhoid bacilli, should be the dose employed for therapeutic inoculation. Leishman [41] has shown that 17,000,000 bacteria cause no appreciable reaction in healthy men. Our aim should be to gauge the amount so as to produce as few constitutional and local symptoms as possible in the fever patient. Where laboratory facilities exist the blood changes which arise after inoculations should be studied by means of opsonic index determination, or by Bordet and Gengou's [42] reaction of fixation of the complement. But if only we are careful to keep the daily dose below the limit at which a reaction
begins to appear, no evil will result from a lack of knowledge of the actual blood condition. The site of the injections should vary; no part should be twice inoculated. The cells, after much stimulation, lose their activity and cease to elaborate elements hostile to the excitant. Thus the mucous membrane of the large intestine is uninfluenced by the *B. coli communis*, while that of the bladder reacts vigorously; cystitis is the consequence, and blood examination shows that specific products are being generated. Then, too, after recovery from enteric fever the typhoid bacillus may become a permanent inhabitant, harmless to its host, of the gall-bladder or alimentary canal and ceases to manufacture anti- enteric substances.

South Africa and Bermuda appear to be the commands in which therapeutic inoculation might be tested with greatest advantage. In the large majority of instances, febrile attacks occurring there among the troops during the enteric season are enteric fever, though many are abortive and are apt to be diagnosed "simple continued fever," "influenza," "bronchitis," "tonsillitis," "diarrhoea," "rheumatism," &c. If, as is suggested, every pyrexial case immediately on admission were treated with daily subcutaneous injections of \( \frac{1}{5} \) of the ordinary preventive dose of anti-typhoid vaccine (easily measured by diluting 1 cc. with 49 cc. of sterile water) the upshot would be—should there be virtue in the remedy—that the number of aborted attacks would be augmented. If care were not taken, it might then happen that the official returns would show no reduction in the case-mortality of enteric fever; but only an increase in the admission rate for "bronchial catarrh," &c., &c. An exact diagnosis by means of cultures from the blood of the patient is therefore much to be desired. As, however, there is considerable reluctance on the part of the physician to draw off 5 or 10 cc. of blood from a person suffering from an apparently trivial ailment Conradi's [43] bile method might be employed, which requires so small a quantity of blood that it may be readily withdrawn from the finger tip. Widal's reaction in most instances is ruled out of court. On the one hand, in the early stages of the fever and in mild attacks, the serum, in dilutions above the limit of error, does not clump the enteric bacillus. On the other hand, the inoculations themselves cause agglutinins to appear in the course of a few days.

Early treatment is insisted upon before gross lesions, such as deep ulceration of the bowel, or profound toxæmia, with the concomitant engorgement of the lungs, have set in.
Treatment of Enteric Fever with Typhoid Vaccine

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[17] Lawson and Stewart. Ibid., December 9th, 1905.
[38] Wright and Reid. Ibid., vol. i., 1906, p. 143.
On the Treatment of Enteric Fever with Typhoid Vaccine

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