THE SPECIFIC PROPHYLAXIS AND TREATMENT OF BACTERIAL DYSENTERY.

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The object of the following brief article on the subject of dysentery is to endeavour to arouse some practical interest in the advances which have been made with regard to the specific prophylaxis and treatment of the disease. A considerable amount of scientific energy has been expended on the subject during the past few years, but the results obtained would appear to have aroused little attention in this country. Only very meagre reports of clinical tests as to the value of specific remedies have so far appeared.

Many opportunities must occur to members of the Naval, Military, Indian and Colonial Medical Services to investigate the causation of outbreaks of dysentery, and in suitable cases to test the value of the methods of treatment which have been suggested as the result of recent experimental investigation. In view of what has been already published by many workers on the subject, such tests appear highly desirable, and these could be most satisfactorily made during small epidemics, and not in time of war, when stress of work must make it extremely difficult to arrive at accurate conclusions as to the value of a particular remedy or method of treatment.

It is almost unnecessary to refer here to the importance of the group of diseases included under the designation "dysentery." "It is one of the four great epidemic diseases of the world."—Osler. In civil life in various regions it constitutes an ever-present danger to life and hindrance to activity, and even where under ordinary circumstances it is comparatively rare, famine or defective food or water supply may cause it to assume a serious epidemic character.

Its gravity in war has been constantly recorded, from the time of the pestilence during the Peloponnesian war, down to most recent times. A striking example of the terrible effects produced as a war pestilence, occurred during the War of Secession of the United States. Woodward states that among the Federal troops the number of deaths due to dysentery and diarrhoea was 37,794, or nearly 30 per cent. of the whole mortality, and among the prisoners at Andersonville the deaths from this disease amounted to 58.7 per
cent. of the deaths from all causes. In many other recent wars the havoc worked by the disease has been hardly less appalling. In the Franco-Prussian War there were 38,652 cases ( = 49 per 1,000), and of these 2,380 died ( = 6'2 per cent. of those affected). Among the officers there were 223 cases with 25 deaths. The death-rate alone, however high, is an inadequate measure of the importance of the disease to armies in the field, for the number invalided is usually very high in proportion to the death-rate.

In this connection it is necessary to refer briefly to some of the most important facts which have been established with regard to the pathogenesis of dysentery. As early as 1873 Loesch had demonstrated the presence of amoebæ in the ulcerated gut in dysentery, an observation confirmed in Egypt by Koch and extended by Kartulis, who came to the conclusion that amoebæ were the sole cause of tropical dysentery. Notwithstanding the fact that amoebæ can occasionally be demonstrated, especially in certain regions, in the dejecta of normal individuals, the important rôle played in the pathogenesis of a certain type of dysentery by amoebæ, probably of a particular species—Amoeba histolytica—is now pretty generally admitted. On the other hand, in many epidemics of dysentery, especially in temperate regions, the most careful investigation failed to demonstrate the presence of amoebæ.

From such observations it became probable that dysentery was not due to a single cause, but that other agents besides the amoebæ may be concerned in the production of the dysenteric condition. Numerous communications were made, suggesting a bacillary origin of many cases of dysentery, but nothing of a convincing nature appeared until the work of Shiga in 1898, when he succeeded in isolating a bacillus, which he regarded as the cause of the disease, from a number of cases during an epidemic in Japan, which from June to December of 1897 claimed 22,300 victims out of 89,000 cases ( = 24 per cent.).

The same organism was found in Germany independently by Kruse, and wherever dysentery epidemics were investigated this bacillus, or bacilli closely related to it, was demonstrated, and its causal relationship to certain outbreaks of the disease is now generally admitted. It appears to be the cause of certain outbreaks of "Asylums' Dysentery" in this country, as was first shown by Eyre. In 1900, Flexner and Strong isolated from dysenteric stools in the Philippine Islands bacilli which they thought at the time to be identical with the Shiga bacillus, but which later were found to differ in several characteristics, such as in possessing the power of
producing indol and of fermenting mannite. That this bacillus has a causal relation to certain outbreaks seems probable, but whether it must be regarded as a separate species or a mere variety of the Shiga type, is still an open question.

Regarding the subject from the point of view of what is known as to its causation, we must clearly separate amoebic dysentery from bacillary dysentery, and under bacillary dysentery it is well provisionally to differentiate at least the two types, e.g., Shiga-Kruse type and the Flexner-Strong type. It is quite conceivable, and is indeed probable, that several organisms besides those referred to may be capable of producing dysentery: but the frequency with which these bacilli occur, and their wide distribution, made it desirable that their presence should be excluded before admitting a pathogenic rôle to another organism.

In regard to the amoebic type we have, so far, no knowledge of a specific prophylaxis or treatment, but in regard to the bacillary type we have a considerable amount of definite information with which I now propose to deal.

Prophylactic Inoculations of Bacillary Vaccines.—Shiga carried out on himself an experiment in this direction on the lines first suggested by Pfeiffer and Kölle in the case of typhoid and cholera. He injected subcutaneously a suspension (about half an agar tube) of bacilli killed by heating to 60° C. for twenty minutes. The local and general reactions following the injection were much more prolonged than in the case of typhoid and cholera inoculations, and Shiga concluded that this method was not likely to be suitable for general use. He therefore carried out some experiments on animals with the object of testing the value of a combined method in which crushed bacillary bodies were injected along with an immune serum. He obtained satisfactory results in the guinea-pig, and found that in that animal the immunity lasted for three weeks.

In man he injected one-half ounce of a killed agar culture along with 0.5 cc. of an immune serum of high value, followed in three to four days by the injection of twice the amount of culture without serum. The reaction by this method was much diminished, and protective substances could be demonstrated twenty to thirty days after the injections. About 10,000 individuals in the area affected by the disease were inoculated by this method, but, unfortunately, the records were unsuitable for statistical investigation. As far as the facts permitted a deduction to be made, it appeared there was no marked effect produced upon the incidence of the disease, but that the mortality fell from 30 to 40 per cent. to almost nil. From
this experience Shiga concluded that more reliance was to be placed upon a serum prophylaxis and treatment than on the employment of bacillary vaccines. It is possible, however, that in chronic cases a combined serum-vaccine treatment on these lines might give good results.

_Treatment by Specific Serum._—Shiga was the first to prepare an anti-dysentery serum by injecting horses with the bacillus which he had isolated. Using 10-20 cc. doses of this serum in 300 severe cases of dysentery the death-rate was about 7 per cent., whereas in 200 cases of the same outbreak which were treated by ordinary methods the death-rate was 22 per cent. The serum appeared to have a distinct effect in reducing the number of evacuations and in shortening the duration of the disease to about one-half.

Kruse obtained similar results in Germany in a small number of about 100 cases. The mortality fell from about 11 to 5 per cent.

Both authors attribute the action of the serum entirely to a bactericidal effect, and the experimental data on animals were of a very convincing nature. Shiga pointed out that this was the first serum which, when injected subcutaneously, had been demonstrated to possess a curative action on a disease of the alimentary canal, and contrasted the results with those obtained by similar means in typhoid or cholera. He laid great stress on the fact that the anti-dysentery serum found a suitable complement in human serum. Neither Shiga nor Kruse made any statement as to the possibility that the bacillus produced a toxin capable of stimulating the animal body to the formation of an antitoxin. Indeed, Kruse states definitely that in this case there was no question of the serum being antitoxic, "Since neither do the bacilli secrete an especially powerful toxin nor does the cause of the disease, with rare exceptions, present the picture of an intoxication."

A most important addition to the knowledge and understanding of the whole subject of bacillary dysentery and a stimulus to the hopefulness of arriving at a successful serum for the treatment of the disease, was given by the work of Todd in the Lister Institute, and Rosenthal in Moscow. These workers independently showed that it was possible to obtain from cultures of the Shiga-Kruse bacillus a soluble toxin, and that the serum obtained by immunising animals with this toxin possessed definite anti-toxic properties. Their results were confirmed by Kraus, and Kraus and Doerr in Vienna.

To refer somewhat more in detail to these results, it was found that the filtrates from cultures about one month old which had
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been grown upon a particular alkaline broth, when tested on rabbits showed a very definite toxic action after a latent period of from one to three days. Severe diarrhoea sets in with paralysis, at first of the hind and then of the fore limbs, and ultimately the muscles of the trunk and neck. The animal loses weight and dies in from one to five days. The chief naked-eye lesions are found in the large gut, which contains a slimy mucous fluid, with congestion, haemorrhages and even erosions of the mucous membrane. The lungs are congested and sometimes small haemorrhages are present. The rabbit and horse are very susceptible to the action of the toxin; the guinea-pig, rat, mouse and monkey much less so. The results with the Shiga-Kruse bacillus were in sharp contrast to those obtained with the Flexner bacillus, in which case under parallel conditions the filtrates possess a very feeble or no toxic action, e.g., whereas 0.1 cc. of Shiga-Kruse filtrate was a lethal dose for a half-grown rabbit, 5 cc. of Flexner filtrate had little or no effect upon an animal of the same weight.

It is impossible here to enter into the subject of the immunisation of horses, &c., suffice it to say that after a fairly prolonged immunisation, either with the toxins from old alkaline broth cultures, or with the bodies of the young bacilli, the serum obtained from horses possesses antitoxic properties of a high order. The fact that bacilli from young cultures on agar were able to stimulate the animal body to the formation of antitoxin, and certain other considerations, led Todd to the conclusion that the toxin was of intracellular origin. In fact, this work on the dysentery toxin and antitoxin is one of the chief grounds which make it extremely difficult to maintain some of the older views as to the sharp line of demarcation between the toxins proper and the endotoxins.

The Properties of Dysentery Serum.—As already indicated, from the outset of the work on this subject it was recognised that the serum possessed bacteriolytic and agglutinating properties towards the homologous bacillus. A serum prepared with the Kruse bacillus appears to have not only specific, but also group bacterioly- sins and agglutinins, which act on the Flexner type of bacillus, though to a much less extent than on the Kruse-Strong type employed in the immunisation. As was shown by the writer, the opsonising action of the serum depends on the bacteriolytic property. From the point of view of therapeutics the antitoxic

1 In the preparation of the Lister Institute serum, both types of bacilli are now employed.
property is probably the most important quality of dysentery serum. To illustrate the high antitoxic value which the dysentery serum may reach, it may be stated that Todd found that when the toxin and antitoxin were mixed some time before injection, $\frac{1}{150}$ of a cc. of serum completely protected a rabbit against twenty certain lethal doses of toxin. The serum is also capable of protecting animals when injected apart from the toxin, and even when injected some time after the toxin, and more recently Kraus and Doerr have found that in certain cases, it is possible by large doses of serum to save the life of the rabbits after the onset of a paralysis which proves fatal to the control animals. From the experimental standpoint, therefore, this serum must be classed along with diphtheria, tetanus and botulismus antitoxins, no serum, with the exception of these, possessing toxin-neutralising properties of the same quantitative order.

The serum has now been used in a considerable number of cases in the human subject in addition to those to which reference has already been made. Rosenthal treated 157 cases with serum. During this epidemic the death-rate of cases treated by ordinary methods was 10-11 per cent., whereas the death-rate with serum treatment was only 4-5 per cent. The quantity of serum given varied from 20-40-60 cc., according to the severity of the case. This is the dosage now generally recommended.

In the Russo-Japanese war Korentchewsky employed Rosenthal's serum in 70 cases with good results.

Barikin treated 59 cases in Manchuria with only 1 death.

Vaillard and Dopter treated 96 cases, all of a severe type, with 1 death. They classify their cases as follows:

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<tr>
<th>Cases</th>
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<tr>
<td>Cases of moderate severity</td>
<td>50</td>
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<tr>
<td>Severe</td>
<td>18</td>
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<tr>
<td>Grave</td>
<td>24</td>
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<td>Extremely grave</td>
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Several other writers, Birt, Lüdeke and others, have treated small groups of cases with favourable results. Kraus and Doerr obtained permission from the Austrian War Ministry to employ the serum in the Austrian Army. They give a brief history of eight cases treated with the serum and refer to other groups of cases in various garrisons. It was impossible to obtain, in many of the outbreaks, reports suitable for statistical analysis, but in all cases the results obtained with the serum produced a favourable impression upon the clinicians. The pain and tenesmus were controlled as by a narcotic, the stools in many cases rapidly assumed a natural
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form, the general conditions were ameliorated, and the period of illness was much shortened.

To sum up, there appears to be a strong case for the use of anti-dysentery serum as a prophylactic and therapeutic agent. The employment of the serum without reference to the nature of the disease is to be deprecated, as it can only lead to disappointing and misleading results. In every case, or at least in every outbreak, it is essential to ascertain the causal agent at work, whether the disease is of an amoebic or bacillary type, and also in the latter case to determine, if possible, to which group the bacillus belongs.

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