

MEDICAL SOCIETY, DIEPPE AREA.

CHEMOTHERAPY IN RELATION TO WAR WOUNDS.

BY COLONEL L. COLEBROOK.

THIS subject was discussed at a recent meeting of the Medical Society of the Dieppe Area, the opening paper being given by Colonel L. Colebrook.

He said that the outstanding lesson of the Great War (in the bacteriological field) was the predominant part played by hæmolytic streptococci in wound infections (Fleming and Porteous, 1919; Stokes and Tytler, 1918-19; Medical History of the War, 1923). Although no critical analysis of deaths was made in the light of bacteriological findings it is probable that this one microbe was responsible for not less than 70 per cent of all the deaths due to infections of wounds. The same microbe gave rise to most of the complications such as erysipelas, cellulitis, and septicæmia, which in turn were responsible for incalculable delay in recovery of the wounded and ultimate impairment of function. He recalled that out of 49 positive blood cultures obtained from men with septic compound fractures of the femur no less than 44 were pure cultures of hæmolytic streptococci (Fleming and Porteous, 1919).

Unfortunately we did not learn during the Great War when and why these infections occurred—whether in most cases the organisms were carried into the tissues at the time of wounding, or whether they were transmitted from case to case in the hospitals, or whether they were due in large measure to dissemination of the microbe by dust or by respiratory tract carriers. The only data obtained (Stokes and Tytler) were that about 15 per cent of a series of 365 wounds were already infected by hæmolytic streptococci on admission to the casualty clearing station (average about twelve hours after being wounded), while a very much larger proportion were so infected when examined after a few days at the Base. (Fleming and Porteous give the figure as 90 per cent for one hospital, and there is reason to believe this was not exceptional.)

These figures suggest that hospital infection played a sinister part, and it may well do so again if the number of casualties to be dealt with is at all comparable. Happily we are in a much better position to-day than we were in 1914 to trace the source of these infections. To that end arrangements have already been made for a co-ordinated effort between the R.A.M.C. and the Medical Research Council. Since it would be difficult to carry out adequate differentiation of many strains in France the Council has established a central laboratory in London for that purpose.

We must also learn how to control these infections. That will be no easy task, but there is great hope in the fact that these streptococci (and, incidentally, some of the gas-gangrene bacilli) have proved to be highly

susceptible to the influence of red prontosil, sulphanilamide and its first cousin sulphapyridine (M & B 693). The striking results obtained in erysipelas, puerperal fever, meningitis and pneumonia, together with the unquestionable effects in experimental infections of animals all over the world, give us good reason to believe that these new remedies will prove of great value in controlling the acute invasive phase of established infections by hæmolytic streptococci.

PREVENTIVE TREATMENT.

Further, it may well be that by their early administration soon after the man is wounded it may be possible to prevent many of these infections from developing or, failing complete success in that, may render them non-invasive, and therefore much less dangerous to life. The war is likely to give us a far better chance of finding out what is possible in that direction than we should have in many years of peace.

Sir Edward Mellanby recently remarked that if such a preventive effect of these chemotherapeutic agents could be clearly demonstrated it would be almost a more important happening than the war itself.

Colonel Colebrook went on to describe the experiments which justify this hope of successful prophylaxis. Mice had been completely protected (Hoare, 1939) by a single injection of sulphapyridine suspended in oil given within a period of twenty-four hours before they were infected with hæmolytic streptococci. Others had shown very good protection when sulphanilamide was given three hours before infection and at intervals after, whereas, if the first dose was omitted, there was no protection. It seemed quite clear that if a certain small amount of sulphanilamide was present in the circulating blood at the time the streptococci reached the tissues they were prevented from causing an acute infection. That was the essential point to keep in mind in considering how to set about prophylaxis in the wounded. Clearly, if the microbes are implanted in the tissues at the time the man is hit, as is almost certainly the case with the gas-gangrene bacilli, we must start prophylactic treatment at the earliest possible moment, and particularly is this necessary in view of the fulminating course of those infections.

In planning our preventive measures against infections by hæmolytic streptococci, on the other hand, we are up against the difficulty that infection is probably not always caused at the time the man is wounded but may occur in hospital during the next few days. A single prophylactic dose given by mouth shortly after the injury will be almost all excreted within ten to twenty hours, and it seems essential, therefore, if we are to maintain the necessary concentration in the blood during the whole period of danger, that its administration must be continued for at least four days. By the end of that time the injured tissues will presumably be walled off by the processes of repair, and infection, if it does occur, will be a much less serious matter. (Attempts have recently been made by Fuller and James (1940) to find a method of securing slow, continuous absorption from the alimentary

tract in man in order to obviate the need for frequently repeated doses, but so far these have not met with much success.)

PROPHYLACTIC DOSAGE.

One could not say dogmatically at present what dosage was required for successful prophylaxis in man as we had no previous experience to draw upon. Rather large doses had been suggested in the first War Office Memorandum (October 11, 1939), but it was explicitly stated that we did not know how they would be tolerated by men suffering from shock and loss of blood. Since that Memorandum was issued new data had come to hand which seem to give us a definite lead as to the dosage required. These data have recently been set out by Fuller and James (1940), together with a suggested plan of dosage designed to give rapid absorption of the drug during the first few hours, and slow, continuous absorption later.

The method advocated was as follows:—

First dose : 1·5 grammes (i.e. 3 tablets of sulphanilamide) dissolved in about 100 c.c. of hot citric acid solution (roughly 1 per cent) or hot lemon.

Second dose : Two hours later, 0·5 gramme (i.e. 1 tablet whole or only partially crushed in order to delay absorption).

Subsequent doses : 0·5 gramme whole or partially crushed, at four-hourly intervals for four days.

Total : 13·5 grammes in four days.

The blood concentrations obtained on these doses in men suffering from shock would have to be checked up to make sure that they corresponded sufficiently well with those obtained on normal men by Drs. Fuller and James. It was important, too, that any toxic effects resulting from these doses should be noted. If they were well borne, but did not suffice to prevent infection, larger doses could be tried later.

In connexion with prophylaxis Colonel Colebrook urged the great importance of trying to reach a definite conclusion. It would be very easy, he said, to reach none at all if the records were incomplete as to the time of starting treatment, the total dosage given each day, the occurrence of gas gangrene, the laboratory findings. He appealed to medical officers in the forward areas and at the Base, as well as to the nursing staff and to laboratory personnel, to co-operate in this investigation. Without that co-operation it could not be carried through.

TREATMENT OF ESTABLISHED INFECTIONS.

The dosage required for the treatment of infections already established would not differ very much from that employed in civil practice. There was some evidence that sulphapyridine is likely to be more effective than sulphanilamide for gas gangrene,¹ and, in order to expedite its absorption, the first three doses (1 gramme each) should be given well crushed and as far

¹ Personal Communication, Dr. D. Stephenson and Miss H. E. Ross.

as possible dissolved in about 100 c.c. of hot citric acid or lemon at an interval of one to three hours. 6 to 8 grammes should be given in the first twenty-four hours and the amount reduced slightly on the next day if the clinical condition was much improved.

For hæmolytic streptococcal infections 1-gramme doses of sulphanilamide should be given four-hourly for the first day or two and the amount reduced *pari passu* with the clinical improvement. For exceptionally severe infections as much as 8 grammes should be given on the first day. The drug should be continued for four or five days after the temperature had dropped to normal and the clinical condition had become satisfactory, but it should *not* be continued after that time just because there were still hæmolytic streptococci in the discharges.

Colonel Colebrook spoke next of the difficulty there was bound to be in appraising the effect of such treatment in wound infections. In the Spanish War different observers had come to very different conclusions because sulphanilamide had been given indiscriminately to all kinds of wound infections—some due to hæmolytic streptococci (presumably) and some not. The same thing had happened when red prontosil was first introduced in Germany and “tried out” in puerperal fever. The obstetric surgeons who used it were not fully alive to the fact that only about 50 per cent of puerperal fever cases are infected by hæmolytic streptococci, the rest being due to a heterogeneous group of organisms, e.g. anaerobic and fæcal types of streptococci, *B. coli*, *B. proteus*, staphylococcus, etc. Subsequent experience of puerperal fever has shown clearly that these heterogeneous infections are influenced very little if at all by sulphanilamide or red prontosil. In every 100 cases, therefore, to whom the drug was given by the German obstetricians (without any discrimination as to the kind of infection) there were about 50 who showed no definite response; while among the remaining 50, i.e. the cases infected by hæmolytic streptococci, about 40 will have been cases who were never very ill and whose prompt recovery therefore left a critical observer in some doubt as to the part played by the new remedy. There remained about 10 gravely ill patients who may be regarded as critical material on which to judge of therapeutic effects. The impression made by a few striking recoveries in this small group may easily have been overshadowed by the failure to show any convincing response among the other 90 cases.

If we were to avoid this pitfall in the present war it would seem to be essential that we should from the outset attempt to restrict chemotherapy to wounds known to be infected by hæmolytic streptococci or by gas-gangrene bacilli (and perhaps some severe infections by staphylococcus). He realized that there was a serious difficulty in doing that because we often could not afford to wait twenty-four hours for the result of a bacteriological examination. Often an examination by film alone would suffice, but if it did not he suggested that treatment should be commenced as soon as there were signs of acute infection, and a swab taken from the wound at the same time. The

bacteriologist should be asked to report as early as possible as to the presence or predominance of hæmolytic streptococci and not to bother about other organisms (except the gas-gangrene bacilli) which might take longer to identify. If hæmolytic streptococci were not present treatment could be discontinued. Such a plan might of course be quite impracticable in times of heavy fighting, but Colonel Colebrook thought that, with some increase of laboratory personnel and equipment, it could be carried out at other times.

Although, with experience of many wounds, the surgeons would probably be able to make a shrewd guess as to the presence of streptococcal infection it would be of incalculable value—at any rate for the earlier period of the war—to get data as to the effect of these new drugs on *bacteriologically verified* infections. That should be our aim.

As regards gas gangrene it was all the more important to correlate clinical signs with bacteriological data because there are indications that some of the organisms of this group are not susceptible to these drugs. Colonel Colebrook hoped that all such organisms isolated from clinically refractory cases would be preserved for differentiation and for determination of their susceptibility to the chemotherapeutic agents *in vitro*.

AGRANULOCYTOSIS.

It has been stated that this condition occurred only rarely as a result of treatment by sulphanilamide and sulphapyridine, but he could not agree with that view. More than 50 cases of complete agranulocytosis had been reported in the literature during the last two years, and as many more of partial destruction of polymorphs (neutropenia). It was certain that for every case reported there were several—probably not less than 10—that were not reported. He himself had heard of nearly 20.

The particulars of published cases strongly suggest that this dangerous condition (it has a mortality rate of about 50 per cent) is closely related to the amount of drug given and the duration of treatment. The average total dose in the recorded cases had been about 50 grammes, and the duration of treatment twenty days. Occasionally, however, much smaller doses and a shorter period of treatment had been recorded. The condition seemed to occur just as often in association with sulphapyridine as with sulphanilamide.

The use of these drugs on a large scale under war conditions called for special vigilance. Wounded men might be given a prophylactic course at the Front and a second course when they arrived at the Base. Possibly a third in England. Such second and third courses appeared to be particularly dangerous. The risk would be greatly diminished if treatment was given only to cases known to be infected by hæmolytic streptococci (or gas gangrene bacilli), and if treatment was stopped soon after the acute febrile phase had passed. It was the general experience that if an infection did not respond to these drugs within four days it seldom did so later.

Recognition of the beginning of agranulocytosis was often difficult—

indeed the diagnosis could only be made with certainty by a rapidly falling white cell count. The onset was usually insidious—a moderate rise of temperature, increasing prostration, and perhaps some headache. The typical agranulocytic angina was often not present, or developed only as a terminal event.

Colonel Colebrook thought that a white cell count and a rough estimate of the polymorphs should be made on every case receiving large doses of these drugs on the seventh day of treatment and, if a second or third course was given, on the first and third days of such courses. Also at any time if the patient's general condition was unsatisfactory or if a sore throat developed.

In conclusion he urged the need for a sense of proportion in this matter. Agranulocytosis was certainly a real danger. On the other hand, these new remedies were unquestionably of great value. Morphine was also a dangerous drug, but that did not prevent us using it and in sufficient amount, when it was required. We had to learn the definite indications for sulphanimide and sulphapyridine, and in many cases receiving large amounts to regulate its administration by periodical estimations of the concentration in the blood and by white cell counts. Such safeguards, he recalled, had not proved an insuperable bar to the use of insulin.

DISCUSSION:

Colonel Weddell said he hoped that the great importance of the surgical toilet of the wounds—removal of devitalized tissues and renewal of skin edges—would not be overlooked in the attempt to prevent infection by chemotherapeutic agents. He also stressed the need for active co-operation of all medical officers, particularly in the tedious business of "paper work" in the attempt to appraise the value of chemotherapy.

Colonel Stott said he had been surprised at the suggestion that many of the streptococcal infections of the last war had originated in the hospitals and were not directly due to the wound. He hoped this would be fully investigated during the present war.

He was not quite clear as to the distinction between the prophylactic and the curative treatment that was proposed. If an infection by hæmolytic streptococci developed in a man who had received, or was receiving, comparatively small doses for purposes of prophylaxis, should he be put on to full doses?

Colonel Colebrook, replying to the first point, said that since the last war it had been clearly demonstrated (Cruickshank, 1935; White, 1936) that wounds discharging hæmolytic streptococci disseminated that microbe through the air around the patient. Presumably the pus, after drying on the skin, readily flaked off in minute particles of "dust." Such particles retained viable and fully pathogenic streptococci for at least ten weeks. When one remembered the conditions in the crowded surgical wards during times of heavy fighting in the Great War it was difficult to see how the

wounds could have failed to become infected by such dust particles even if infection was never transmitted from case to case in the process of daily dressing.

The work of Sir Almroth Wright in the last war had shown that the hæmolytic streptococcus was better adapted for establishing itself in wounds than any of the other common bacteria because the serous fluids of the wound provide an ideal culture medium for it.

Unless the number of such infections could be kept very much lower by preventive chemotherapy and successful primary suture, it would seem almost inevitable that the surgical wards in the present war would again become hotbeds of streptococcus infection.

Replying to the second point raised by Colonel Stott he admitted that some confusion must arise owing to the fact that the prophylactic treatment had to be continued for several days. If during that period—or subsequent to it—signs of an active invasion by hæmolytic streptococci did develop, he thought the dose of drug should be at once increased to the ordinary scale given for the treatment of established infections.

Colonel Myles asked if there was any evidence as to the efficacy of local applications of sulphonamide derivatives. He had been impressed by one instance in which the spraying of a soluble sulphonamide preparation had been followed by a remarkably prompt disappearance of hæmolytic streptococci and meningococci from the nasopharynx.

Colonel Colebrook, replying, thought it was unlikely that local applications would have any beneficial effect in the upper respiratory tract. Although sulphanilamide had a direct bactericidal action in the presence of body fluids, that effect was usually only manifested after exposure of the organisms to the drug for several hours. It was difficult to imagine that fluid sprayed into the nasopharynx would remain there in effective concentration for more than a few minutes. It was, moreover, improbable that such fluid would find its way into the depths of tonsillar crypts where hæmolytic streptococci were believed to lodge.

The local application of sulphanilamide in suppurating wounds has sometimes been proposed, but it is very doubtful if it would have any beneficial effect (Fleming, 1940). On the other hand the remarkable success claimed by Jensen, Johnsrud and Nelson (1939) in the treatment of compound fractures by a sulphanilamide pack prior to suture (i.e. before suppuration occurs) suggests important possibilities in connexion with war wounds. This is being investigated.

Lieutenant Kanaar asked for more precise information as to "treatment in the febrile phase." He recalled a case of meningitis in which the temperature had come down under treatment but had continued to show irregular fluctuations between normal and 100° F. for ten days or more. The patient had by that time had about 40 grammes of sulphanilamide. Was it wise to continue treatment in such a case?

Colonel Colebrook said that he sometimes saw cases (usually of puerperal

fever) like that cited by Lieutenant Kanaar, and he suspected that they were often infected by an organism which was partially or completely insensitive to the action of sulphanilamide. (In five instances that insensitiveness had been confirmed by an *in vitro* test.) He thought it was not worth while to continue treatment in such cases. And it was doubtful whether anything was gained by switching over to sulphapyridine since streptococci which were insensitive to one were usually insensitive to both drugs. This was, however, an aspect of chemotherapy which needed more investigation. He hoped that if medical officers came across cases in which prophylactic treatment of a wound had been given a good trial and had failed they would send him the organism for examination.

Major Nevin asked what evidence there was as to the relative efficacy of sulphanilamide and sulphapyridine.

Colonel Colebrook said that the results of experimental infections in animals indicated that the two drugs were of about equal value against hæmolytic streptococci, and his own experience of human beings led to the same conclusion.

With regard to infections by gas gangrene bacilli, there was too little evidence at present to permit of any conclusion. In severe staphylococcal infections, too, sulphapyridine seems to be the more effective.

Major Harrison asked what was the present view about cyanosis occurring during treatment by these drugs. Colonel Colebrook said that severe cyanosis was seldom seen nowadays when care was taken to exclude eggs from the diet and to avoid sulphate aperients. The mild degrees of cyanosis could be disregarded and treatment need not be discontinued.

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