CHEMOTHERAPY

YESTERDAY, TO-DAY AND TO-MORROW

THE title which I gave for this lecture was too ambitious. It would require a whole series of lectures to do it justice. I must limit it to chemotherapy of bacterial infections, but even that subject is too large for one lecture, so I propose to restrict myself for the most part to chemotherapeutic happenings of which I have first-hand knowledge.

Bacterial infections have existed since time immemorial, and physicians, in all ages, have tried to deal effectively with them. It has been our good fortune to have lived in an era when many of these infections have, for the first time, been brought under control, and there is promise of more advances in the near future.

Until the middle of last century there was practically no knowledge of the bacterial nature of the infections, so before that time everyone was working in the dark, and many and curious were the prescriptions used in the combat against

bacterial infections; but we shall get no profit by discussing these.

In the consideration of almost every branch of bacteriology we go back to Pasteur and the latter half of the nineteenth century. Pasteur proved that certain fermentations were due to the action of microbes and that microbes were living objects which did not arise *de novo* from the putrescible material but were descendants of previously existing organisms. Pasteur himself did not do any serious work on chemotherapy, but his earlier bacteriological work stimulated Lister, who had putrefaction of wounds very much at heart, to engage himself on the subject.

There are some who use the word chemotherapy in a very limited sense to cover those methods in which the chemical is administered in such a way that it gets into the blood and attacks the infecting microbes through the circulation in concentrations sufficient to destroy them or modify their growth. This is too narrow a definition, and I shall use chemotherapy to cover any treatment in which a chemical is administered in a manner directly injurious to the microbes infecting the body. In this latter sense antiseptic treatment comes under chemotherapy—call it local chemotherapy if you like. The same general laws govern the treatment whether it is local or systemic, but there are

certain particulars in which one has to draw a distinction. There are many chemicals used locally which are so poisonous to the human organism as a whole that they cannot be used for systemic treatment, but large numbers of these, although they had considerable vogue in the past when perhaps there was nothing better, are practically useless as chemotherapeutic agents except in the prophylactic sense. On the other hand, there are some chemicals, e.g. the sulphonamides, which are powerful agents for systemic treatment but which are frequently of little use when locally applied to a suppurating area, as their action is neutralized by substances occurring in the pus.

If a chemical is to be effective in the treatment of established infection it is necessary that, in addition to killing or inhibiting the growth of the microbes on the surface, it should be able to diffuse into the tissues to reach the microbes there. In a septic wound there are, of course, microbes in the cavity of the wound, but far more important are those which have invaded the walls.

Lister, like all other surgeons of 90 years ago, was struggling with the problem of septic wounds. To him, Pasteur's work came as a ray of light in the darkness. Putrefaction was due to living microbes which were introduced from outside. He set to work to prevent them being introduced.

He cleansed his hands and his instruments, and treated them with chemicals, and he used a carbolic spray to kill bacteria in the air and prevent them reaching his operation wounds. In this way he revolutionized surgery.

That was prophylactic chemotherapy. Lister himself recognized that carbolic acid, which was his standby as an antiseptic, was very poisonous to the tissues. There are times, however, when if it is possible to kill all the bacteria in an infected area with a chemical it may be worth while to sacrifice certain tissues locally, but the usefulness of such toxic chemicals is very strictly limited.

As a result of the success of Lister's antiseptic treatment a large variety of chemicals were introduced as local chemotherapeutic agents for the treatment of localized infections. In time bacteriology was put on a sound basis, and the antibacterial effect of these chemicals could be tested in the laboratory. In the early days of the laboratory investigation of these antiseptics (or local chemotherapeutic agents) little attention was paid to anything but their action on bacteria in a watery medium. This resulted in very high values being given to substances like mercuric chloride, which could be diluted about half a million times before it lost its power of inhibiting the growth of bacteria when tested in watery medium, but which was

largely 'quenched' in the presence of serum or blood.

But none of these chemicals had much effect in destroying bacteria once they had invaded the tissues. I commenced medicine in the early years of this century. Then Lister's methods were rather discredited—asepsis had taken the place of antiseptics for prophylactic chemotherapy, but for the treatment of infections which were already established, a great variety of chemicals were used. Carbolic acid, boric acid, mercuric chloride, silver salts, iodine, etc., were used extensively on septic conditions, but there did not in most cases appear to be any striking benefit except perhaps in some superficial infections. These chemicals were used quite empirically and were, I suppose, a relic of the antiseptic days when they had proved valuable in prophylaxis. They failed in treatment. They were either non-diffusible, or if they were diffusible they poisoned the tissues more than the bacteria. One of the first things I learnt in the casualty room was not to put a carbolic compress on a septic finger or carbolic gangrene was likely to result.

Then came the war of 1914–18. The aseptic surgeons were suddenly presented with masses of wounds, all of which became infected. The primary infection was from the soil and the soldiers' clothing and was largely anaerobic, but after a week or

more in hospital this was replaced by the usual septic infection of civil life—mainly staphylococci, streptococci and coliform and diphtheroid bacilli.

Into these wounds all manner of chemicals were poured in an attempt to destroy the infecting microbes. It was not so difficult sometimes to get rid of the majority of the microbes in the cavity of the wound—they could for the most part be washed out by simple irrigation with normal saline—but none of the chemicals had much action on the bacteria in the infected wound walls.

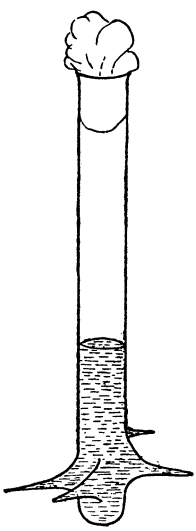

Fig. 1. Artificial wound.

I might here show you a simple experiment which illustrated the inability of chemicals to sterilize even the cavity of a wound. From a test-tube some small processes were drawn to imitate the irregular processes in the cavity of a war wound. The tube was now filled with serum and infected with the usual bacteria which were found in wounds. Here we had an irregular infected cavity, but there was no possibility of the microbes invading the walls (Fig. 1). The 'artificial wound' was 'dressed' by inverting the

tube and allowing the fluid to escape. This was replaced with an antiseptic which was allowed to remain in the tube for various times up to 24 hours, after which it was poured out and replaced by serum. The tube was then incubated, and next day there was a copious growth of bacteria with all the chemical antiseptics tested. The antiseptic had been unable to diffuse into the processes and kill the bacteria there, so as soon as the antiseptic was removed they grew out again and contaminated the whole tube.

Another observation made in the 1914–18 war is of some importance in local chemotherapy. In 1917 probably the most favoured method of treatment of a septic wound was the Carrell Dakin treatment. Dakin's fluid (sodium hypochlorite) was instilled into a wound every 2 hours. I had an opportunity of studying the length of time that Dakin's fluid remained active in a wound; I found a cup-shaped wound into which I could put a fluid and withdraw the whole of it after any interval. When Dakin's fluid was left in such a wound for 10 minutes its potency had diminished below the limit at which it was antiseptic in serum. It followed from this that for 1 hour and 50 minutes out of every 2 hours there was no effective chemical antiseptic in the wound. But Dakin's fluid had another quite unexpected action. After it had

been applied it caused a marked increase in the transudation of fluid from the walls of the wound which persisted for some time after fluid was removed.

Fig. 2 illustrates this increased transudation. Incidentally the number of living bacteria was not

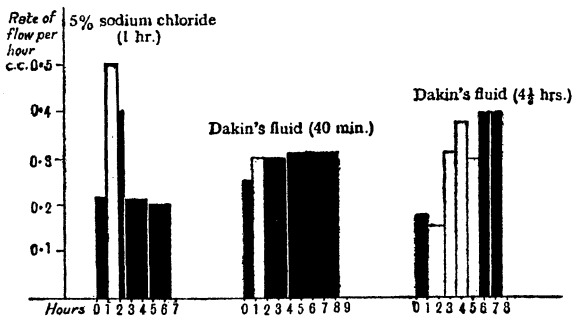

Fig. 2. Increased transudation. Dakin's fluid. Black columns = before and after. White columns = during application.

reduced in the exudate after the application of Dakin's fluid for $4\frac{1}{2}$ hours.

I suggest that the chief virtue of Dakin's fluid was not direct antiseptic action, but that it lay in this power of stimulating the exudation of fluid from the infected walls of the wound, thus draining the oedematous tissues just as did hypertonic saline solution, which was another favourite dressing for a septic wound. But Dakin's fluid *in vitro* in the

absence of serum or pus was a powerful antibacterial agent, so all its benefits in treatment were ascribed to its direct antiseptic action.

It is desirable in the investigation of the action of these chemicals to see how long they remain active in the body, and before we class them as chemotherapeutic agents we should see if possible whether the apparently beneficial effect is due to a direct antibacterial action.

I have said that Lister recognized the local toxic action of his favourite antiseptic, carbolic acid, but the toxic action of many of its successors was not so obvious and was sometimes forgotten.

Later, and especially in the war of 1914–18, some notice was taken of the action of these chemicals on cells and especially on leucocytes, as it was not difficult to test the effect of a chemical on leucocytic function. Most usually it was the phagocytic power of the leucocytes which was tested, but the methods adopted did not always give a true picture. The effect of the chemical on bacteria was tested by its power to inhibit growth and its effect on leucocytes by its power to inhibit phagocytosis. This at first sight seems a perfectly good method, but actually the chemical acts on the bacteria during a period of hours, whereas in the phagocytic experiments the maximum time of action was 15 minutes. When blood is mixed with

bacteria phagocytosis takes place very rapidly, and even in 5 minutes the cells will take up large numbers of microbes. That being so, if a chemical is added to the mixture which does not have a *rapid* lethal action on the leucocyte the latter continues to phagocyte the bacteria, and if the observation is ended after 15 minutes quite a false idea is obtained as to the destructive action of the chemical on the leucocyte. Acriflavine is a good example of this. It is a slow-acting bactericidal and leucocidal agent. If its antileucocytic power is tested only for 15 minutes it has been found that it requires a dilution of 1 in 500 to reduce the amount of phagocytosis by 50 %. If, however, the chemical is allowed to remain in contact with the blood for 5 hours before the phagocytic test is made, it is found that a 1 in 500,000 dilution will cause a 50 % reduction in the amount of phagocytosis. As it takes a 1 in 200,000 dilution to inhibit the growth of bacteria the 'Therapeutic index' calculated after 15 minutes' exposure of leucocytes is 400, whereas if the time of exposure had been 5 hours (a more reasonable time) it would have been 0·4—a considerable difference.

In 1924 I adapted Wright's slide-cell method to show in one experiment the action of chemicals on bacteria and on leucocytes. Dilutions of the chemical were made in normal saline, and to these