Editorials.

THE TREATMENT OF ANAEROBIC INFECTIONS WITH SULPHAPYRIDINE AND WITH IMMUNE SERA AND THE PROBLEM OF SYNERGIC ACTION.

THE dramatic success of the sulphonamide series of drugs in the treatment of certain infections caused by aerobic organisms and their use as substitutes for serum therapy has tended to obscure the potential advantages that might accrue from combined treatment with drug and immune serum. W. W. Henderson and P. A. J. Gorer have been interested in the theoretical and practical aspects of the problem of combined action in so far as it might be concerned in the prophylaxis and therapy of infection caused by certain spore-bearing anaerobes. They were encouraged to pursue the problem as experiments seemed to indicate that sulphanilamide and its related compounds are of value in the treatment of gas gangrene, and the advent of the war gave the subject a practical importance.

They consider that the genesis of infection with a spore-bearing organism is determined by the physico-chemical conditions governing germination of the spores. Once germination of the spores has taken place the course of the disease is determined not only by the products of bacterial metabolism but also by the capacity of the vegetating organism to invade the healthy tissues of the host. The species included in the gas-gangrene group of spore-bearing anaerobes vary greatly in this respect. Those of low invasive capacity remain relatively localized near the original site of tissue damage, although the necrotizing toxin extends the area for their proliferation. The truly invasive species such as *V. septique* and *Cl. chauvœi*, and possibly certain strains of *Cl. welchii* are not confined within the extending area of necrosis and may advance into apparently healthy tissue. There are three lines of approach to prophylaxis or therapy: (1) Control of bacterial infection; (2) neutralization of accumulated toxin; or (3) a combination of both. The control of infection by neutralization of accumulating toxin is to be regarded as a secondary line of defence; it enables the body to mobilize antibacterial and repair mechanisms that will deal effectively with a traumatic lesion supporting bacterial proliferation. Antitoxic measures for the control of infection with species of high invasive capacity are problematical in effectiveness; the final issue depends on the ability of the host to muster an antibacterial defence and this is greatly influenced by the route of infection. A most interesting result of experiments is the difference between the combined action of sulphapyridine plus antitoxin, and that of antibacterial plus antitoxin serum. The slight but direct bacteriostatic

action of the sulphapyridine and the neutralizing action of the antitoxin gives time for the natural defence system to be mustered, and it is this third factor in the presence of the other two agents which brings about the striking result.

In the *Journal of Hygiene* for May, 1940, W. W. Henderson and P. A. J. Gorer record their experiments on the treatment of gas gangrene anaerobic bacteria with sulphapyridine alone or in conjunction with antitoxin or antibacterial serum. These workers used *Cl. septique*, the infecting dose of which could be controlled, and the intradermal and intramuscular routes. They found that the drug alone was fairly effective in controlling intradermal infection, but when given prophylactically and in continuous dosage it could only save half the mice infected intramuscularly. Sulphapyridine had a slight action on intradermal infection of *V. welchii*, but none at all on intramuscular infection of this organism. It had no neutralizing effect on the toxins of either *Cl. welchii* or *V. septique*. On the other hand, antitoxin was very successful in saving mice even when given six hours after intramuscular infection of *Cl. welchii*. Intradermal infection with *V. septique* was used to test the possible synergic effect between drug and antitoxin and antibacterial serum, and the experiments were so planned that any of these agents would only protect 5 to 10 per cent of the infected animals. It was found that sulphapyridine plus antitoxin produced a survival rate of 88 per cent compared with only 7 to 8 per cent in the controls. The drug plus antibacterial serum produced 72 per cent of survivals. A combination of antibacterial and antitoxic sera saved only 15·5 per cent of infected animals. In *Cl. welchii* infection the combined action of antitoxin and sulphapyridine produces a notable synergic effect, but the evidence on this point is less clearly defined.

In intradermal infection with *V. septique* the combined action of sulphapyridine and antitoxin or of sulphapyridine and antibacterial serum effects a saving of life much greater than would be expected if a mere summation effect is in question. A similar effect is observed in intramuscular infection provided the administration of the drug is sufficiently prolonged. No such synergic effect is produced by the combined action of antitoxic and antibacterial serum.

A very important observation was that one dose of antitoxin combined with continued administration of sulphapyridine raised the survival rate of mice infected intramuscularly with *Cl. septique* from 0·20 to 70 per cent.

Henderson and Gorer point out that their results were obtained with single strains of *Cl. welchii* and *V. septique*, and that there is considerable difference between the toxigenicity and invasiveness of different strains, particularly of *Cl. welchii*. There appears to be no doubt that considerable synergic action exists between the drug and antitoxin ; the antitoxin probably neutralizes the bacterial toxin, while the drug exerts a bacteriostatic action on the organism itself.

In view of these results it has been suggested that every wounded patient in whom gas gangrene is diagnosed or suspected should receive an adequate

dose of polyvalent antitoxin. It should be given intravenously at the earliest possible moment, one therapeutic dose for the suspected case and for the established case three to five doses combined with 6 to 9 grammes of sulphapyridine daily until the infection is controlled.

ACTION OF ANTISEPTICS ON WOUNDS.

L. P. GARROD, in the *Lancet* of May 4, 1940, draws attention to the selective action of antiseptics which differs with bacterial species. Spore-forming bacilli and tubercle bacilli are exceptionally resistant owing to their impenetrability. *Ps. pyocyanea* and *Streptococcus fæcalis* are also very resistant for no obvious reason. The antiseptic may exhibit unequal degrees of activity peculiar to itself against different types of micro-organisms. These extreme inequalities are only seen in antiseptics such as dyes, which act in high dilutions; their effect on certain bacteria is due to a peculiar affinity. Phenol, on the other hand, is a protoplasmic poison and acts equally on most types of non-spore-forming micro-organisms.

Staphylococci are intensely susceptible to the violet dyes; streptococci are a little less so; most Gram-negative bacteria are highly resistant to these dyes. The acridine compounds, on the other hand, exert their most powerful action on hæmolytic streptococci, staphylococci being less susceptible. The pneumococcus is peculiarly susceptible to optochin. *Ps. pyocyanea*, which flourishes in the presence of many antiseptics, readily succumbs to dilutions of acetic acid which other bacteria can resist.

This selective action can only be taken into practical account in an established infection in which the responsible organism has been identified. Garrod thinks that in this sphere of therapeutics effective treatment is much less feasible than prevention.

If an antiseptic is not wholly lethal, certain resistant organisms begin to multiply. Therefore, it is advisable to discontinue an antiseptic if it does not achieve its effects after several days.

The form in which an antiseptic is applied is important; solutions of phenol in water are highly toxic, but a 5 per cent solution of phenol in olive oil is bland and unirritating but inert. To dissolve or emulsify an antiseptic in oil usually prevents its diffusion into a watery medium and destroys its effect. The acriflavine emulsion of the B.P.C. is another example; this is inert.

The incorporation in a semi-solid oily basis in the form of bipp deprives iodoform of its power to restrain bacterial growth. Most ointments are ineffective, but if made up with vanishing cream they act better. The proper vehicle for an antiseptic to be applied to a wound is water, and the solution should, if possible, be rendered isotonic.

If the possibility of prophylactic treatment of wounds is considered impartially Garrod thinks it must be admitted that prophylaxis is a very

different thing from the treatment of an established infection of a wound and should be easier to achieve. The number of bacteria is comparatively small and they are in a wound cavity more or less accessible to treatment from without. From observations on experimental wounds and by analogy with the lag period in cultures, it can safely be concluded that the proliferation of the bacteria and invasion of the tissues will not occur for two hours or more. During this period an antiseptic will have an easier task than on the following day, when the tissues are involved and no known antiseptic is capable of reaching the now enormous numbers of invading bacteria. The prevention of infection does not necessarily require that all the bacteria contaminating a wound must be destroyed. It has been demonstrated by experiment that there is a minimal infecting dose varying with the virulence of the bacteria at the time and the resistance of the host; a number less than this can be dealt with by the body. Exposure to no more than sub-lethal concentrations of antiseptics for only a few minutes greatly reduces bacterial virulence; this effect is known to be produced by acriflavine on streptococci.

Garrod considers there are two policies, either of which might be adopted for the prophylactic treatment of wounds. First, the effect on the tissues in the wound may be disregarded for the sake of securing complete disinfection. An instance of this was the application of pure phenol as in the early days of the Great War. Methods so drastic have the drawback of leaving necrotic tissue liable to further infection. There is more to be said in favour of using antiseptics not so grossly toxic but rapid and powerful in their action on bacteria; among these the less toxic coal-tar derivatives, such as cyllin, izal, and dettol, deserve consideration. Used in adequate strength they kill bacteria in a few minutes even in mixtures containing blood, and they cause no gross damage to the tissues. They may kill such leucocytes as were in the wound. These are few and easily replaced, and it is clear from clinical experience that there is no really disastrous effect on the cells of skin, connective tissue, or muscle. No other class of antiseptic combines rapidity of effect with adequate activity in the presence of blood. Dyes and acridine compounds act in blood but slowly; the halogens act quickly but not in blood. In the category which accepts microscopic cell damage for the sake of more efficient disinfection must be placed the use of such dyes as crystal violet and brilliant green.

The alternative policy is to insist that adequate disinfection shall be combined with minimum toxicity to the tissues so that no damage may be done to specialized cells. There is no answer to this demand except in the acridine compounds. Experiments have shown that these compounds have been able to prevent infection when experimental wounds in animals are inoculated with virulent bacteria, and that prolonged action is necessary to secure adequate disinfection is the main drawback of these substances which in the ideal treatment should remain in the wound cavity for an hour or more. To apply a dressing or to pack with gauze soaked in the antiseptic

is not ideal because the affinity of the cotton for dyes leads to the retention of the antiseptic in the substance of the dressing. Solutions of acridine compounds can be injected interstitially without ill-effect, and thorough infiltration of the tissues round a small but dangerously infected wound is good treatment. It is particularly indicated for punctured wounds sustained accidentally during septic operations, the track of which is narrow, inaccessible to external appliances, and perhaps untraceable.

Where an antiseptic cannot reach it cannot act, and excision is the only measure which will deal effectively with such a condition. Where excision has to be delayed antiseptic treatment should be used for what it is worth.

The effect of antiseptics applied to infected wounds depends on two factors : The depth from the surface which the bacteria have reached, and the depth to which the antiseptic can follow them—penetration of tissue. Studies of the penetration of tissues by antiseptics are few and incomplete, but such as there have been seem to show that a fraction of a millimetre is the limit for most of them, so it is foolish to expect any effect on spreading cellulitis, on suppuration spreading on fascial planes or between muscle bundles, or on gas gangrene. The control of actively spreading infection is the sphere of systemic chemotherapy with sulphonamide compounds.

If no active spread is taking place in a wound but healing is delayed, the surface may be formed by superficial sloughs or by granulation tissue exuding pus. Antiseptics applied to such wounds prevent the access of further infection, deodorize the wound, and mechanically cleanse it. The process of mechanical cleansing is well served by solutions containing chlorine or liberating oxygen, both of which tend to disintegrate necrotic material. The shedding of sloughs may be accelerated by stimulating the exudation of fluid and the good results claimed for certain antiseptics may be due to it. More profuse fluid exudation can be obtained by applying hypertonic saline solutions ; sulphate of soda is said to be the most active. Garrod considers that the depth to which infection extends in different types of non-spreading infection of wounds is imperfectly understood and well worthy of study. Our incomplete knowledge on this point and of the capacity of various antiseptics for different types of tissue makes it difficult to decide whether any substantial part of the effect is due to influence on the bacteria beneath the surface of the skin of the wound. He believes it is much more likely that in granulating and suppurating wounds the observed effects—e.g. the disappearance of *Ps. pyocyanea* after the application of acetic acid—are due to the destruction of bacteria which are simply multiplying in the discharge from the wound and are not in the tissues at all.

A serous or purulent exudate which collects in a cavity forms an admirable culture medium for some types of bacteria, and it is doubtless useful to get rid of them, but this does not imply the sterilization of tissue. Whatever antiseptic treatment is adopted it should be strictly limited in duration. The killing of bacteria is final, and if it is not accomplished within a day or two there is no reason why it ever should be, and one good reason

why it should not: the fact that exposure to sublethal concentrations of antiseptics produces in bacteria an increased resistance to them. Long-continued application is also contra-indicated because of its effect on the growth of reparative tissue. Clinical experience suggests that continuous irrigation with a weak hypochlorite solution by the Carrel-Dakin method may with advantage be continued rather longer than the application of other kinds of antiseptic, especially in dealing with large and dirty wounds. It is also reasonable if one antiseptic fails to try another for an adequate but limited period. Garrod writes that to take this somewhat sceptical view of the antiseptic treatment of infection in wounds is not to deny that such treatment can be highly effective in other situations. The response of thrush to the application of violet dyes is almost miraculous, presumably because the infection is more superficial and therefore more accessible; some superficial skin conditions are also amenable to such treatment. The depth to which the infection extends must be considered the paramount factor in determining whether surface applications can control it. He considers that the undeserved contempt for antiseptics which is now so common is largely based on beliefs which arose during the Great War when the almost universal judgment on experience with casualties in France was that antiseptics had failed. There are particular reasons for this failure which forbid the application of this judgment to the treatment of wounds as a whole. Perhaps the chief of these was that treatment was so often necessarily delayed. It cannot be too strongly emphasized that the prevention of infection in wounds is entirely different from its treatment when infection has become established, and prevention in this sense is only possible for an hour or two after the infliction of the wound. Invasion of the tissues then begins and disinfection of the wound cavity is of no avail. Much of the use of antiseptics in France was not prophylactic, but the treatment of a developing infection which could not often succeed. Another cause of failure is to be found in the characteristics of the gunshot wound; it consists of a long narrow track through muscle or viscera at the end of which may be a foreign body, a shell fragment, and a dirty piece of clothing. The deeper parts of such a wound are inaccessible. These two factors will always counteract the success of antisepsis in military surgery and were mainly responsible for the failure of such treatment in France. If anything more were needed to explain it some of the methods used furnish the answer. Strong phenol, strong cresol pastes, and formalin were freely used in the early part of the war, and it was not until the introduction of Dakin's solution and of the flavines that any method came into general use which was at all likely to do more good than harm.

It must be remembered that military casualties coming to this country now may have received prophylactic doses of sulphanilamide or of sulphapyridine, and it is hoped that septic wounds will be materially less in this war than in the last.

Garrod draws attention to the fact that there is no generally accepted

method of testing the disinfecting power of an antiseptic to be used in wounds or of assessing the degree of damage it will do to exposed tissues. The general adoption of such methods and the acquisition through them of comparable data for all antiseptics in common use would clarify what is now a confused position. Distinct from immediate damage is the effect of prolonged application on the ratio of healing; this is readily susceptible to experimental study.

The method of the prophylactic treatment of wounds in the experimental animal which has so far awarded all the prizes to the acridine compounds, needs to be more widely applied; the position of other dyes, of the organic mercury compounds, and of emulsified antiseptics derived from coal-tar would be clearer if data obtained by this method were available for them.

Finally, any study of disinfectant action, whether *in vitro* or *in vivo*, can be usefully amplified by embracing bacteria other than the pyogenic cocci.

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Notes