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THE VALUE OF ANTISEPTICS IN THE CONTROL OF BACTERIAL INFECTIONS*

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The question, How far can infections by pathogenic organisms be influenced for the benefit of the host by means of antiseptics? incidentally involves inquiry into the properties of antiseptics which suit them for such purposes, and also into the methods of their application. By "antiseptic" is understood a substance of ascertained chemical constitution harmful to the activities of micro-organisms. The problem, then, is one of chemotherapy in the sense defined by Ehrlich. Restricting consideration to the ordinary bacteria, we shall see that success has been chiefly obtained where the drug can be brought into close contact with the site of a localized infection in a wound or natural cavity. Therefore the chemotherapy of bacterial infections is at present most intimately associated with surgery. Generalized bacterial infections are still practically beyond the reach of antiseptics. This admission must not be interpreted as the confession of failure: the antiseptics now available have very great therapeutic potentialities, and the advances already made open up still wider prospects. It must be remembered, too, that until recently little has been done to correlate biological and chemical work on the problems. In order to clarify the present position the scientific origin of antiseptic treatment will be traced, and the limitations of the older antiseptics will be noted.

Lister and Antiseptic Therapy

Lister was without doubt the first to employ antiseptics on a scientific basis. Fortunately, his guiding principles are authoritatively summarized by the late Sir Hector Cameron in the Dr. James Watson Memorial Lectures (1907), which had been submitted for revision to Lister himself.

"It was hard, perhaps, to appreciate the fact that carbolic acid was not used by Lister (as it undoubtedly had been previously used by others) as 'a local dressing of wounds' with the view of acting directly, and with a specific healing influence, on the wounded tissues, but rather that it was employed to destroy germs which, if they reached the wound in the living state, had the power of preventing the natural processes of repair. . . . His constant aim was to place wounds, as far as possible, in conditions resembling those of subcutaneous injuries, free from the access of external morbid agencies, as well as from direct irritation by foreign substances."

Lister, it is true, applied carbolic acid to the soiled tissues exposed in a compound fracture for the express purpose of destroying pathogenic bacteria which had

obtained access to the living body. He must therefore be considered the scientific pioneer in this form of therapy. It should be borne in mind, however, that his attitude was obviously that of one who unwillingly employed an extreme measure to meet a desperate situation. In addition, he was aware of the uncertain efficacy of carbolic acid when used for this purpose, since he observes: "while we endeavour to purify the wound with strong carbolic lotion we cannot be certain of entire success."† The harmful action of carbolic acid on living tissues appears to have been well known to Lister; he did not contemplate its introduction into the abdominal cavity because "it must be in itself a very desirable thing to avoid the direct application to the peritoneum of strong and irritating antiseptic solutions." Further, as Sir Hector Cameron says:

"When dealing with abscess, no antiseptic was ever introduced into the cavity at all. It was far otherwise with many of those who counted themselves amongst his disciples and imitators. Not perhaps thoroughly appreciating the scientific facts which were the basis of the treatment, they were unable to divest themselves of the old idea, that, whatever was used in the treatment of a wound, was necessarily intended to have some specific effect on its healing. It could not, therefore, be brought too freely or too often into contact with it. They filled kettles with carbolic solutions, and poured them over wounded surfaces or injected these same solutions into all interstices of wounds with syringes, while abscesses, empyemata and the like were freely syringed out in the same manner at the time of operation, as well as at every subsequent dressing."

The other antiseptics contemporaneous with carbolic acid—namely, the perchloride and other salts of mercury, boric acid, iodoform, and iodine, etc.—all suffered from the same disadvantage that if employed in concentrations sufficient to damage bacteria their general effects as "protoplasm poisons" on the tissues of the host tended to become prominent. Now it must be remembered that Lister's condemnation of the application of antiseptics to the tissues referred to those substances of which he himself had experience. I am not aware that he ever denied the possibility of finding antiseptics suitable for this purpose.

Need for Therapeutic Antiseptics

The result of Lister's teaching was that operations of election were regularly performed without the super-vention of wound infections. This safe conduct into the texture of the body was the prerequisite of the miracles

† In view of this uncertainty, Lister in such cases came to employ in addition iodoform, which he regarded as probably acting not directly on the bacteria, but by inducing chemical changes in their toxic products as suggested by Behring.

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of modern operative surgery. No blessing, however, seems altogether unmixed, and the fact that aseptic wounds can be inflicted at will with so great a measure of confidence has led to undesired consequences which in all probability were entirely unforeseen.

First, the occurrence of infection in a wound of election has now commonly come to be regarded as due solely to some fault in the preparations for, or in the performance of, the operation. In order to realize the error of this generalization one need only recall the "cryptogenic" infections with pyogenic bacteria in deep tissues altogether apart from any gross trauma. Even gas gangrene sometimes arises at a site remote from the point of entry of the organisms (see Learmonth, 1924). If bacteria can settle, multiply, and set up a focus of disease at a site without any preceding bruise or other gross local pathological condition, it is clear that they are even more likely to behave in this way where the tissues have been damaged by the surgeon's knife. A wound, even when inflicted under the strictest aseptic conditions, constitutes a site of lowered resistance, and is therefore liable to the lodgement of organisms which may reach it from the blood or lymph streams. Consequently, there is certain to be a proportion of septic accidents following operations of election which are due to infection acquired from within, and which cannot be avoided by a technique which aims merely at hindering access of bacteria from that surface whose continuity is breached by the surgeon. Here there is obvious need for a tissue antiseptic. Omission to guard against such endogenous infections must be due to a mistaken interpretation of Lister's teaching.

Again, where the operator is compelled to approach his objective through a naturally infected surface, such as the conjunctiva or a mucous membrane, strong solutions of the old antiseptics cannot be used, unless, of course, a diffuse caustic effect is desired. It is perhaps on this account that the occasional occurrence of meningitis after operative procedures on the nose and related cavities is sometimes viewed as an inevitable accident. Another undesired consequence has been a failure of interest in improving methods of treating wounds which are already infected before coming under the surgeon's care, probably because a feeling of responsibility for such infections has been wanting. The attitude reflected in many surgical textbooks to-day is that in the treatment of infected tissues it matters little what antiseptic is used, since its function is quite subsidiary to that of appropriate surgical manipulation—in other words, excision, drainage, and the natural defensive powers of the tissues will do all that can be expected.

Thus, after the pioneer work of Lister and Koch, therapeutic investigation of antiseptics did not advance rapidly. Behring, Koch, and Stilling pointed out the powerful antiseptic action of certain basic aniline dyes, and Stilling (1891) recommended methyl-violet for treating infections of the conjunctiva and joints. Also extremely potent new organic antiseptics were described by Bechhold and Ehrlich (1906). But these researches attracted little attention.

Stimulated by Ehrlich's fundamental work on the chemotherapy of protozoal diseases, and by observations made by Churchman and Dreyer, Kriegler and Walker on the properties of methyl (gentian) violet, Browning and Gilmour (1913) studied more thoroughly relations between chemical constitution and antiseptic action among the organic dyes, including several of the acridine series. Two of the latter, proflavine (3 : 6 diamino-acridine) and tryptaflavine (acriflavine) were put at our disposal by Ehrlich; the last was also examined independently by Shiga for antiseptic action on *V. cholerae*. The need for improving the treatment of war wounds led

to renewed activity, and subsequently many substances have come into use; a number of these are a great advance on the older types of antiseptics as therapeutic agents. It is impossible to deal with them all in detail here, but I shall review the experimental evidence of the efficacy of antiseptic treatment and indicate briefly the clinical bearing of the facts.*

Antiseptic Therapy of Recent Infections in Wounds, Serous Cavities, etc.

In order to obtain decisive evidence regarding the curative action of antiseptics it was necessary to make controlled observations on animals. Various organisms and methods of inoculation have been used. As regards imitating pyogenic infections of man, a difficulty is the tendency for the infections in laboratory animals to become quickly generalized.

However, an infection of recent skin wounds in guinea-pigs with a culture of virulent *B. diphtheriae* affords a very suitable test object for therapeutic agents (Feiler). The bacilli do not become generalized, so that in this important respect the condition resembles that usual in human wounds contaminated with pyogenic organisms. At the same time conclusive proof of the effect of treatment is obtained, since in the untreated controls death occurs in forty-eight to seventy-two hours. The following procedure was adopted (Browning and Gulbransen, 1925).

Experimental Technique.—When the animals were under the influence of a general anaesthetic two parallel linear cuts, each about 3/4 inch long and 1/3 inch apart, were made in the shaved skin of the abdomen in the long axis of the body. The strip of skin between the cuts was raised from the deeper structures, and also that for about 2/5 inch on either side of the incisions, so as to form pockets, there being practically no bleeding, and a quarter of a young, well-grown agar culture of virulent *B. diphtheriae* was rubbed into the wounds and the pockets. Periods of 3/4 to two hours were then allowed to elapse before treatment. This consisted in washing out the wounds with 1 c.cm. of a water solution of the substance under test, and swabbing the pockets with a small pledget of cotton-wool which had been soaked for several minutes beforehand in the same solution. The animal was placed on its back during treatment, and the whole procedure lasted for seventy-five seconds. Finally, any fluid not absorbed by the tissues was allowed to drain away and the surrounding skin swabbed dry. There was no further treatment, and all survivors were kept for at least three weeks.

Results.—The outcome of the above experiments was that out of twenty-two inoculated animals treated with acriflavine (1 in 100 to 1 in 2,500) twenty-one survived, whereas of seven treated with carbolic acid (1 in 20 to 1 in 100) five died, and of fourteen whose wounds were washed out with either 0.85 or 5 per cent. salt solution all died. Iodoform in the form of "bipp," rubbed into the infected wounds, failed to save the life of all three animals so treated. Acriflavine is about fifty times more potent than carbolic acid, as measured by the concentrations of the two substances required to bring about cure. Further, it has been shown that the curative effect of acriflavine is not caused by destruction of diphtheria toxin present in the culture used for inoculation, but is due to action on the bacilli (Braun).

Other Investigations.—Virulent streptococci, either in the form of cultures or of material (blood, etc.) from infected animals, have also been used to inoculate recent skin wounds in mice (Reinhardt, Schiemann and Wreschner, Weise, Collier and Bernhagen). In such experiments failure of the therapeutic agent is shown by the animals dying of septicaemia. Here also a single brief application of one of the new antiseptics half to one hour or later after

* Bennett, Blacklock, and Browning (1922) give a critical discussion of earlier clinical observations.

inoculation has preserved the animals from an otherwise fatal infection. It is noteworthy that Weise found excision of the surface of the wound one-quarter to two hours after inoculation to be without beneficial effect. When the inoculation was made into deep wounds of muscles, treatment was less effective than in more superficial wounds. Reinhardt obtained similar results with recent skin wounds in guinea-pigs inoculated with pneumococci and treated by washing of the wounds with the antiseptic half an hour later. The most effective of a series of substances tested was acriflavine; on the other hand, 1 in 20 carbolic acid and tincture of iodine were without perceptible action, but mercuric chloride 1 in 1,000 prolonged the life of the animals. The controls, whose wounds were washed out with saline, died in two to seven days. Infection of the cornea in rabbits, produced by injecting virulent pneumococci, has been sterilized by optoquine instilled into the conjunctival sac or injected subconjunctivally (Ginsberg and Kaufmann). In guinea-pigs inoculated intramuscularly with soil containing pathogenic anaerobes of the gas gangrene group and *B. tetani*, Brunner, Gonzenbach, and Ritter (1918, 1924) showed that the resulting fatal infection could be prevented by antiseptic treatment, even when begun many hours afterwards. All organisms are not equally susceptible in the tissues, however. Thus, Hata (1932) failed to influence recent wound infections with *B. oedematis*, although this bacillus was not specially resistant to the antiseptic *in vitro*, and the acridine compound which he used was effective against other organisms *in vivo*. The troublesome local septic infections of the skin which tend to occur in scarlet fever patients, owing to contamination with discharges from the nose or ear, have been regularly prevented by treatment of the latter with acriflavine (J. W. Howie, unpublished). It should be noted that in the experiments on wound infections referred to above, the physical conditions were the same in the treated animals and the controls. This is very important, since, as Preobajensky showed, an alteration in the physical conditions of an infected wound may of itself determine the outcome of the infection.

Peritoneal Inoculation.—Where the inoculum is introduced into the peritoneum, from which generalization rapidly occurs, the therapeutic problem is obviously difficult. Nevertheless, very considerable success has been obtained in mice infected with virulent streptococci and treated after an interval, usually one hour, by an intraperitoneal injection of a suitable antiseptic. Untreated controls, or those which received only physiological saline intraperitoneally, died from septicaemia in twenty-four to forty-eight hours. The following results were obtained with the most effective substances tested by Browning, Cohen, Ellingworth, and Gulbransen (1931).

Therapeutic Agent	Cures Treated
2 (p-dimethylamino-anil) 6-methylallyl-acetyl amino-quinoline methochloride ($\frac{2}{3}$ to $\frac{1}{3}$ of tolerated dose used) ...	34 out of 47
2 (p-dimethylamino anil) 6-n-caproylamino-quinoline methochloride ($\frac{2}{3}$ to $\frac{1}{3}$ of tolerated dose used) ...	53 out of 82
Acriflavine ...	13 out of 21

Together
87 cures
out of 129
treated

Untreated controls: Of 125 animals inoculated all died in 24 to 48 hours.

Many other substances were without effect, including carbolic acid 1 in 300 (the largest tolerated dose). The general result also of similar experiments by others is that an appropriate antiseptic cures an infection which without it will develop into a fatal septicaemia. The objection may be raised that the interval between inoculation and treatment is short, but in small animals the infection progresses rapidly, so that the period is a considerable fraction of the whole illness.

Treatment of Local Suppurative Processes

Such lesions are not easily produced experimentally in laboratory animals, there being, as a rule, a marked tendency for the infection to spread. Morgenroth and his co-workers tested the effect of the local injection of antiseptic in sterilizing the tissues and preventing the development of a "phlegmon" in mice after subcutaneous inoculation with pyogenic streptococci. But the results tend to be irregular, owing largely to the uncontrollable factor of the individual animal (Browning and Gulbransen, 1928). In experimental empyema in the rabbit, produced by inoculating one pleural sac with streptococci, Gay and Morrison, on injecting acriflavine into one or both pleurae, and in some cases also aspirating the exudate, did not succeed in saving the life of the animals. Although the pleural contents were sometimes nearly sterilized, regrowth and spread of the organisms occurred. Eggerth, employing similarly a mixture of proflavine and sodium oleate with the same object, obtained more promising local results; but here again generalization of the infection vitiated the effects of the treatment.

Observations on treatment of the human subject are seldom adequately controllable, but when in one individual separate lesions, similar in size, severity, and situation, are treated by different methods, differences in the results can justifiably be attributed to the treatment. Graham's (1925) case is convincing in this respect. Three areas on the back of the hand and forearm in which the whole depth of the epithelium had been destroyed by contact with boiling fat, were dressed with acriflavine (1 in 1,000) within an hour after the injury. Two days later granulation tissue was present in the base of all the burns, and there was no suppuration and little discomfort. Then on one of the areas a dressing of wet boric lint was substituted, while the others continued to be treated with acriflavine (1 in 5,000), each dressing being renewed once daily. After six days' application of boric acid the area so treated was actively suppurating and extremely painful, whereas the others were free from sepsis and showed healing in progress. Accordingly, boric acid was replaced by acriflavine, and after three days further this area also was free from pain and suppuration. The results of Turner (1919) in septic and fetid conditions of the gums also have the decisive character of an experiment. In cases where the bad odour was readily detected at several yards' distance from the patient, the breath, twenty-four hours after commencing treatment with acriflavine, was free from smell.

Infections of the urinary tract may be considered here, since local application of the antiseptic can be secured either from beneath by injection, or from above by administering by mouth or intravenously substances which are excreted in the urine. The observations are almost wholly clinical, and, as regards the second method, the substances usually employed are so feeble in their action that doubts regarding their efficacy are not surprising. Infections of the kidney, whether a gross obstruction such as a calculus in the pelvis or ureter be present or not, probably cannot be sterilized by any urinary antiseptic at present available. It is possible, however, in healthy men to procure unfailingly the secretion of urine antiseptic toward both *B. coli* and staphylococcus after the administration of acriflavine combined with alkalization* (Davis and Sharpe). This fact does not appear, however, to have been much utilized—for example, as a measure preparatory to operation on the urinary tract. The value of antiseptics in the therapy of gonorrhoea at an early stage seems not to be doubted, but much more work is required to discover an ideal treatment.

* A difficulty is the tendency towards nausea and catharsis

The secretion of antiseptic bile is still to be achieved. Intrathecal antiseptic medication in meningitis has not been shown definitely to yield favourable results. It appears so far impossible to influence the bacterial flora of the alimentary tract by antiseptics (Garrod, 1926 ; Graham, 1932 ; Browning, 1933).

General Infections

Koch originally attempted to treat septicaemia by an antiseptic. Mercuric chloride being highly inimical to *B. anthracis*, he injected guinea-pigs repeatedly with it both before and after inoculation with the bacilli. The animals, however, died like the untreated controls, in spite of having received in proportion to their weight an amount of the mercury salt sufficient to prevent all growth of the organisms in a broth culture. Morgenroth and Levy cured experimental pneumococcus septicaemia in mice by optoquine. With this outstanding exception, all attempts to cure a general bacterial infection by such means have failed under experimental conditions, although the bactericidal powers of the blood or serum may be raised temporarily by the injection of certain antiseptics. In experiments already mentioned recent streptococcal infections of the peritoneum were cured by an intraperitoneal injection of antiseptic when organisms were already present in the blood of a control animal. This, however, may merely mean that a certain degree of bacteraemia does not preclude cure provided that the chief source of infection can be effectively dealt with.

Properties of Therapeutic Antiseptics and their Mode of Action

The new therapeutic antiseptics are mostly dyes. This property is objectionable to many, and doubtless when more is known regarding relations of chemical constitution to antiseptic action colourless substances fitted for the purpose will become available. Further advance depends chiefly on the synthesis of still more suitable compounds. It is important, therefore, to define as far as possible those characters of an antiseptic which indicate its therapeutic value. The essential property, of course, is that the harmful action on bacteria shall exceed that on the tissues.

Effect on Bacteria.—Rapidly of bactericidal action is not essential. Organisms, although continuing to be viable, may nevertheless be profoundly altered in their pathogenic action by contact with the antiseptic, so that the natural defensive mechanisms of the host can come into play effectively. Accordingly, favourable therapeutic results are likely to be due as a rule to co-operation between the drug and the tissues. As an example of this, a concentration of antiseptic sufficient to cure a recent peritoneal infection with streptococci, or to prevent infection when injected as a mixture with the organisms, has been found to take some hours to kill the cocci *in vitro* (Browning, Cohen, Ellingworth, and Gulbransen, 1931).

The following observation illustrates well this problem of reducing virulence (J. W. Howie, unpublished). A strain of streptococci of which a two-thousand-millionth of a cubic centimetre of fluid culture injected intraperitoneally regularly killed a mouse, was treated with acriflavine in gradually increasing concentrations *in vitro*; finally, although the organisms still grew vigorously, the injection of 1/2 c.cm. of the undiluted culture was harmless.

Again, selective action on one species of bacteria as compared with another may have to be reckoned with, so that the nature of the infecting organism may decide what antiseptic is to be used. However, many of the new antiseptics—for example, acriflavine, proflavine, rivanol, quinanil (Armitage and Gordon), and mercurochrome-220, as well as brilliant-green—all act fairly uniformly on

various common pyogenic organisms, although *B. pyocyaneus* tends to be resistant to many. A valuable character of certain of the new antiseptics is that their powerful action on bacteria is not reduced by serum. Substances such as mercury compounds and chlorine derivatives do not merely suffer dilution by serum, but their antibacterial property is enormously weaker in serum than in a watery medium. Among substances not inactivated by serum are acriflavine, proflavine, rivanol, quinanil, and many other analogous compounds prepared by Professor J. B. Cohen and his co-workers. When inactivation by serum occurs frequent renewal of the antiseptic is necessary.

Mutual Effects of Tissues and Antiseptics.—Several effects must be considered. Fixation and consequent inactivation of the antiseptic by tissues and pus occurs to some extent probably with all antiseptics. Graham (1928) measured the absorption of acriflavine, carbolic acid, and mercuric chloride by minced muscle soaked in solutions of these drugs. Mercuric chloride is powerfully fixed, the other two less so; on the other hand, acriflavine alone of the three is fixed by cotton, and this must be allowed for when applying wet dressings, otherwise one may merely treat the wound with dyed cotton instead of antiseptic solution. It is possible that fixation of the antiseptic by the tissues in an infected area may sometimes be advantageous, since in this way a depot may be created from which continuous action on the organisms will be maintained. Morgenroth attributed the greater therapeutic effect of one substance as compared with another on streptococci in the subcutaneous tissue to such differences in fixation, although both were equally antiseptic *in vitro*.

The liability of tissues to injury from an antiseptic may be measured in various ways. Thus, intravenous injection shows the action on the animal as a whole or on any specially susceptible organ. Unless a substance is intended for intravenous administration, however, this test of toxicity may be too exacting, because a substance like brilliant-green, which is very toxic intravenously, is tolerated safely when applied to the open surface of a wound. Subcutaneous or intramuscular injection also indicates general toxicity provided absorption takes place; these methods, further, show the local action on tissues. But here again the effect of introducing the substance into the closed tissues may differ from that in an open wound; for example, brilliant-green solution subcutaneously in the rabbit causes marked persistent local oedema, but when used to dress a wound does not have this effect. Action on delicate surfaces may be ascertained by instilling a solution into the conjunctiva of an animal and retaining it there for some minutes, or by injecting it into the peritoneum.

In all such tests the varying behaviour of different species and even of different individuals must be considered. It is important to avoid irritation of delicate surfaces which harbour bacteria; thus antiseptics applied in a concentration sufficient to irritate the nasal passages in rabbits led to lighting up of latent pasteurella infection. A number of the new antiseptics are distinguished by the relatively high concentrations required to cause marked irritation or damage of the tissues as compared with the low concentrations which harm bacteria. Tests on cells *in vitro* have been proposed; the difficulty is to relate them to conditions *in vivo*. Some observers have concluded from such experiments that the tissues are always more vulnerable than the bacteria, and so antiseptic treatment has been condemned by analogy. In actual fact, as has already been seen, infections which would otherwise be certainly fatal can be cured by antiseptic chemotherapy. The method of tissue culture has also been utilized, whereby bacteria and fragments of embryonic tissue are

incubated together for twenty-four hours in a nutrient fluid containing the antiseptic. In this way the concentration of the drug inhibiting proliferation of the fibroblasts and that preventing growth of the bacteria can be ascertained. Of all substances tested, including carbolic acid and mercuric chloride, the only ones which inhibit streptococci in a concentration lower than that damaging to the tissue are acriflavine and other acridine and quinoline compounds (Mueller, Hata). According to Hata, tryptaflavine (acriflavine), rivanol, and certain new acridine compounds permit proliferation of the tissue cells in a concentration several times greater than will prevent growth of streptococci. The significance of these results cannot be disregarded, since conditions *in vitro* are much more favourable for the bacteria than for tissue cells. On the other hand, we do not know the relative vulnerability of the fibroblasts of chicken embryos and the mesoblastic elements of adult human and other mammalian tissues. A highly desirable action of an antiseptic would be to penetrate cells without harming them and to inflict damage on organisms in their interior; probably this does not occur. Failure also to act on bacteria embedded in masses of dead or devitalized tissue was apparently a serious disappointment, which led some surgeons from their experience with severe war wounds to discount the newer antiseptics.

A direct method of investigating action on tissues consists in examining histologically the base and edge of wounds under treatment with the antiseptic, as von Eicken originally did at the early stage. Bennett, Blacklock, and Browning showed that when acriflavine and proflavine are used so as to control sepsis there need be no inhibition of healing. Blacklock, in sections of human material taken during such treatment, found mitoses in various classes of granulation tissue cells and in skin epithelium, as well as active growth of young bone, at depths of 0.018 to 0.2 mm. below the actual free surface. Other properties of antiseptics on tissues may be utilized advantageously—for example, the solvent effect of hypochlorites (eusol) on fibrin and necrotic material.

In the case of fairly resistant tissues, like skin, certain non-irritating antiseptics are available which can be applied in very concentrated form, as for preparation of the skin before operation—for example, mixture of brilliant-green and crystal violet (Bonney and Browning, McLeod and Brown); mercurochrome-220 (Young, White, and Swartz); hexylresorcinol (Leonard and Feirer); and "dettol" (Colebrook and Maxted). Some of these are also used in the vagina.

Summary

1. Several types of compounds are now known which, as compared with the old antiseptics, possess a much higher antibacterial power relative to their toxicity for mammalian tissues. A further advantage of certain of these is that serum does not neutralize their antibacterial action.

2. There is conclusive evidence that by their use recent experimental infections with streptococci and other organisms localized in wounds and serous cavities can be cured, whereas saline washings or injections are without effect. Thus a true chemotherapy of local bacterial infections has been realized. Under similar conditions substances such as carbolic acid or mercuric chloride are much less effective, or fail altogether. Curative action on established local suppuration has also been demonstrated under controlled conditions.

3. Antiseptics intended for therapeutic use must not be considered *en bloc* or selected solely on the basis of their ability to kill rapidly some test organism *in vitro*. Each must be examined as regards selective action on various bacteria in protein as well as watery media *in vitro*, and as regards effects on tissues *in vivo*. Such tests give valuable indications, but the chemotherapeutic efficacy of a substance is finally determined by its

influence on the pathogenic action of organisms in an infected host. More extended investigation on these lines is required.

4. The most successful clinical application of antiseptics is likely to be the prevention of infection in tissues liable to contamination, or recently contaminated with bacteria. But limitation of both the extent and duration of established pyogenic infections, and hence of the various consequences, can also be attained. Necrotic or devitalized tissues cannot be sterilized. Accordingly antiseptics must be used as an addition to established physical (operative, etc.) measures and other forms of therapy. Details of procedure cannot be transferred by analogy from one animal species to another, and the surgeon must therefore work out the best methods of utilizing the properties of the new antiseptics in human treatment.

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According to L. Klein (*Thèse de Paris*, No. 121) some authorities are of the opinion that rice beds have little to do with the spread of malaria. Italian writers, particularly Alessandrini, have even suggested the establishment of rice beds as a prophylactic method against the disease. Although rice beds bring about an extraordinary increase in anopheles, these mosquitos, according to Alessandrini, do not give rise to malaria. On the other hand, the recrudescence of malaria in certain regions where it was very rare before the establishment of rice beds shows that the culture of rice is inadvisable as an antimalarial measure. As, however, rice beds cannot be suppressed without causing serious economic loss to the country, other measures must be taken to prevent the spread of malaria, such as periodical drying of the rice bed for four days every fortnight to destroy the larvae, the introduction of fish for the same purpose, and the prohibition of rice beds in a radius of less than 1,000 metres of a village. Unfortunately, as the natives in the colonies are the slaves of tradition, it is very difficult to make them adopt the smallest modifications as regards the culture of rice, so that the problem of malaria and rice fields is still unsolved.