

Antiseptics*

Work done for the British Medical Research Committee in the Pathological Department, Edinburgh University

By Theodore Rettie, D. SC.

IN January, 1915, the National Insurance Medical Research Committee, at the request of the War Office, issued an appeal to the various medical schools to institute research on several problems which had been encountered in the medical service at the front. One of the most urgent requirements was a reliable antiseptic for the treatment of heavily infected wounds, with special attention to spore-bearing organisms. Professors Lorrain Smith and Ritchie at once organized several sets of workers to investigate the various problems, under their own direction. The work on antiseptics was carried out by Professors Dr. A. Murray Drennan, now Professor of Clinical Pathology in Otago; Dr. W. Campbell, now a Captain in the R. A. M. C., stationed at Alexandria, and myself.¹

It may seem strange that over 40 years after the introduction of antiseptic surgery by Sir Joseph Lister no ideal antiseptic has been devised for such emergency treatment: the explanation, I think, is to be found in the tendency of modern surgery to leave as much to the recuperative power of the patient's own body as possible. In preparing for operation the surroundings of the patient are rendered as sterile as possible. Instruments, swabs, dressings, everything that will come in contact with him, are sterilized by heat, in fact, nothing that is not sterile is allowed to touch him. Under such conditions the only antiseptic necessary is some iodine solution to sterilize the patient's skin, and lysol or such preparation in which to place instruments after use. In accident cases where the wound is already infected, the injured tissues are carefully dissected out under chloroform and the wound cleansed with some strong antiseptic, most often with 5% aqueous carbolic acid, Lister's original antiseptic, or, by some of the ultra-aseptic surgeons, with large douches of sterile saline (0.85% salt solution—this is known as normal saline as its osmotic pressure is equal to the pressure of the plasma of the body). Such procedure, though successful with a limited number of patients, obviously cannot be applied in a casualty dressing station; the wounds are always contaminated: they are deep, often ramifying, and may contain pieces of clothing or splinters, all presumably carrying infection. To meet such conditions powerful remedies are necessary, but they must be discriminatingly powerful; microbes which are vegetable cells must be killed, both vegetative forms and spores, which are much more resistant. At the same time the animal cells of the tissues must be damaged as little as possible by the antiseptic; free drainage for all discharges from the wound must also be maintained.

In opposition to the antiseptic method there is what has been called the physiological method of wound treatment, introduced by Sir Almroth Wright. The wound is treated with a hypertonic saline solution, i. e., a solution having an osmotic pressure higher than that of the plasma. As a result of this, fluid is rapidly poured out by the tissues, the idea being that the microbes are thus washed out of the wound and at the same time destroyed by the bactericidal properties of the lymph.

In support of this method the argument was advanced that any antiseptic damages the tissue to which it is applied to such an extent that the value of it as a destroyer of bacteria is lost, and the dead cells and coagulated albumin which the antiseptic leaves in the wound are a fertile source of further trouble. By hypertonic saline treatment this difficulty is avoided. With these two principles in mind, our object was to find an antiseptic agent thoroughly efficient as a killer of bacteria and spores, and at the same time harmless from the point of view of the wound tissues.

Our first step was to test the comparative efficiency of all the antiseptics in general use. It is obvious that it is impossible to make a definite statement as to the value of an antiseptic for wound treatment from its behavior under laboratory conditions. Most elaborate experimental methods have been devised in the endeavor to fix a standard by which antiseptics may be tested, but further research has shown that so many factors enter into the efficiency

problem that test tube methods have come to be regarded more or less as a compromise. For instance, Chick and Martin² have shown that what might be called mass action, i. e., the actual number of bacteria exposed to the action of the antiseptic in the test tube, has a very important bearing on the efficiency. The presence of organic matter other than the bacteria has naturally a protective action in favor of the bacteria: various mixtures of bacteria with blood serum, whole blood, pus, muscle extract, etc., have been employed to reproduce as far as possible conditions likely to be met with in a wound. For our tests we decided to use pieces of heavily-infected tissues which were exposed for definite periods to a large volume of the antiseptic solution. The tissue after treatment was washed free of the antiseptic with successive quantities of sterile water, and in cases where it was deemed necessary any residual antiseptic was neutralized by appropriate chemical methods. The tissue was then put into a tube of sterile broth and incubated: readings were taken at 24, 48 and 72 hours.

The antiseptics tested were those in use at the military hospitals in Edinburgh and others which have been more or less in general use: they were phenol, acrosyl, kymol, chinolol (oxyquinoline potassium sulphate), hydrogen peroxide, mercuric iodide, tincture of iodine, potassium permanganate 4%, methylated spirit, turpentine, salicylic acid, sodium salicylate, methyl salicylate (oil of wintergreen), glycerin, bleaching powder, bleaching powder and hydrogen peroxide (for nascent oxygen), eau de Javelle, boric acid. Our test proved very drastic: of the above only bleaching powder, 10% solution, eau de Javelle (10% sodium hypochlorite), 5% phenol, and the mixture of bleaching powder and hydrogen peroxide had any effect in delaying or inhibiting growth, and the first two were decidedly ahead of the others. The hypochlorites were thus proved, as has often happened before, to be the strongest antiseptics in general use. There are other points decidedly in their favor. Bleaching powder is cheap, easily procured anywhere, and above all it cannot be classed as a dangerous poison. On the other hand, pure *Liquor calcis chlorinatae* and eau de Javelle are very drastic remedies and on account of their strong alkalinity and high chlorine content (about 3% available chlorine) the tissues will not stand their continued application: for this reason they have never come into general use, though they have both been used with great success on occasion. For instance, in 1846 Semelweis, an Austrian physician, stamped out an epidemic of sepsis in his hospital in Vienna by using bleaching powder. Pasteur used *Liquor calcis chlorinatae*, and I am informed by Sir James Russell that when he was a medical student in this university Professor Spence constantly used it. Our problem thus reduced itself to getting bleaching powder into a solution or powder that could be applied to open wounds without damaging the tissues unduly.

Following our original method, i. e., with infected tissues, and using mixtures of varying proportions of boric acid and bleaching powder with small quantities of water, we found that with equal quantities of each we got a most pungent smelling paste which had no difficulty in sterilizing the tissue and, on the other hand, apart from bleaching, did not seem to damage it as much as was expected. We also found that the gas (hypochlorous acid) given off by this mixture was capable of sterilizing highly infected tissue, provided it was allowed to act long enough: in some of the experiments two hours was sufficient. This mixture, therefore, gave promise of high value as a wound dressing, and I shall have occasion to refer to it later. Solutions prepared from this mixture were next tested and very interesting results were brought out; the bactericidal efficiency of the solution was greatly increased; instead of 3.5% available chlorine, as in *Liquor calcis chlorinatae*, one-tenth of that amount gave very satisfactory results, the free hypochlorous acid proving a much better germicide than the calcium salt.

Further test experiments were carried out with anthrax spores, one of the most virulent and resistant of pathogenic organisms; we were gratified to find that our solution in a strength of 0.35% available chlorine killed the spores in one minute.

Turning next to the action on living tissues, working

first on rabbits, then on ourselves, then on patients in local hospitals, we were soon convinced that hypochlorous acid in a solution such as ours could be applied to tissues in a strength hitherto unsuspected. Large quantities of the solution can be applied to extensive wound surfaces, and may be freely introduced into the peritoneum or pleural cavity without producing any toxic effect; indeed the mixed powders may be introduced into wounds and even into the peritoneal cavity without damaging the tissues; such treatment has been found very effective in grossly infected wounds.

Pure hypochlorous acid in aqueous solution always contains free hydrochloric and chloric acids due to spontaneous decomposition, one molecule of hypochlorous acid being oxidized to chloric acid at the expense of other two molecules which are reduced to hydrochloric acid. Both are very strong acids and therefore pure hypochlorous acid is not suitable for wound treatment.

By adding boric acid to chloride of lime in the proportions above stated we have produced a solution containing calcium bichlorate, an acid salt of extremely low hydrogen ion concentration; on mixing such a solution with one containing hydrochloric acid, the acidity is reduced as the free H⁺ ions are taken up by the boric ions forming H₃BO₃; the acidity of the solution therefore cannot rise above the dissociation constant for boric acid, which is very low.

By this adjustment various advantages have been secured; the alkalinity of the chloride of lime has been reduced, the full effect of the free hypochlorous acid has been secured, and the solution cannot become unduly acid. In virtue of this balance it follows that the solution can be applied freely to the tissues of the body, and that a considerable quantity can be injected into the circulating blood without harmful effect.

The high germicidal value of pure hypochlorous acid solutions was demonstrated in 1903 by Andrews and Orton.³ In test-tube experiments they found that very weak solutions of hypochlorous acid, 1 part in 100,000, would kill pathogenic organisms in one minute, but when applied to solutions containing organic matter as well as bacteria they found the hypochlorous acid so rapidly destroyed that they did not evolve any method of applying the solution as a practical antiseptic.

Putting all the above observations together we fixed on the following as safe antiseptics:

The powder, equal weights of chloride of lime and boric acid. The solution, prepared by shaking up 25 grms. of the above mixture in one liter of water and filtering off the sediment; this solution contains about 0.26% hypochlorous acid. The powder we named Eupad and the solution Eusol—words derived from the initial letters of Edinburgh University Pathology Department.

A simple and convenient method of preparing small quantities of Eusol is to make it up from *Liquor calcis chlorinatae*, that is 10% chloride of lime; this solution, contrary to the statement in the Pharmacopoeia, keeps very well if stored in a cool dark cupboard. I have kept it for months in the laboratory with a very small loss of chlorine. This solution may be made in quantity, say, two liters, filtered clear, and the chlorine content determined; the amount necessary for one liter of Eusol is easily calculated; with a good chloride of lime this should be about 125 c.c. which is diluted to one liter, and shaken with 10 grms. of boric acid; the solution remains clear.

For testing we recommend N/10 sodium arsenite solution; this solution keeps better than sodium thiosulphate; it is also better for testing bleaching powder, as chlorates do not interfere with the result, as they do in the hydrochloric acid and potassium iodide method.

Another hypochlorite solution has also been introduced as an antiseptic. It is known as Dakin's⁴ solution and contains sodium hypochlorite and sodium bicarbonate; its action is much the same as that of Eusol but it is decidedly alkaline.

As Eusol is a most powerful oxidizing agent it is evident that its value as an antiseptic will soon be reduced in contact with organic fluids such as are en-

¹F. W. Andrews and K. J. P. Orton. *Cent. f. Bakt.*, 1903-4, 35. Abt. 1, pp. 645 and 811.

²Dakin. *B. M. J.*, 1915, 2, 318.

*From the *Journal of the Society of Chemical Industry*.

¹Lorrain Smith, Drennan, Rettie, and Campbell. *B. M. J.*, 1915, 2, 129.

²Chick and Martin. *Journal of Hygiene*, 1908, 8, 654.

countered in an open wound; therefore in order to bring any effective solution into contact with the organisms hidden in the depths of the wound, large quantities must be used and the solution got down to the lowest recesses and pockets. To accomplish this, surgeons have various appliances with rubber tubes branching from a common source of supply; this method was applied most successfully with Eusol by Captain Miles⁵ in Edinburgh and also by Captain John Fraser⁶ in France. A similar method has been advocated by Carrel, who worked with Dakin's solution at Compiègne, and constitutes the Carrel-Dakin⁷ method of wound treatment.

We have further observed in open wounds a distinct outpouring of lymph on the application of Eusol, thus combining the advantages of the hypertonic saline treatment with the killing power of the hypochlorous acid; here also the nontoxicity of the solution tells strongly in its favor; there are no toxic by-products at all. Carbolic acid is an excellent antiseptic, but if applied to a wound in unlimited quantity it very soon produces necrosis and may even produce symptoms of general poisoning. The cresols and emulsions containing them precipitate a sticky film of resinous matter in the wound, clogging it and preventing free drainage.

In the course of our preliminary experiments on the effect of Eusol on live tissues we found that large quantities, as much as 40 to 50 c.c., could be injected into the blood stream of rabbits without injuring the animal; following up this line of investigation, with a view to attacking sepsis in the blood, we have met with a considerable measure of success. We applied this method of treatment in the first instance to a case of puerperal septicæmia in the Maternity Hospital in this city.⁸ The patient was suffering from an extremely grave form of blood poisoning; the treatment was completely successful.

Following on this, Captain John Fraser, R. A. M. C.,⁹ applied the same treatment to soldiers suffering from the acute toxæmia arising from wounds infected with the gas-producing organisms—*Bacillus Welchii*, *B. sporogenes*, etc. These organisms, which cause what is known as gas gangrene, owing to the fact that they produce large quantities of gas inside the tissues, are the scourge of the casualty clearing stations; they are spore-bearers and therefore difficult to kill and the spores are present everywhere.

In certain types of gas gangrene toxæmia, Captain Fraser found intravenous Eusol as strikingly successful as in our first case, but in others it did not seem to have any effect; and this has been the experience of all workers who have employed the method. Sir Herbert Waterhouse¹⁰ in his report from Anglo-Russian Hospitals, says: "We entertain the highest opinion of its value as a life-saving method in many apparently hopeless cases of septicæmia and pyæmia." This treatment was the subject of much investigation under our own care at the Sick Children's Hospital in Edinburgh. A paper on the subject was published in the *Edinburgh Medical Journal*¹¹ this summer. As a result, we found that evidence of benefit was recorded in cases of lung infection, such as broncho-pneumonia, empyema, abscess of lung; in toxæmia from appendicitis, and in one case of toxic diarrhoea, also in cases of chronic meningitis. No benefit accrued in cases of rheumatism or in tuberculosis.

The problem we are now engaged on is to find out why in certain bacterial infections we can help the recuperative powers of the body and in others we cannot. We may be acting on a toxin produced by the bacteria and circulating in the blood, or we may destroy some toxic agent formed by the blood itself, or may merely stimulate a protective reaction in the body fluids. Many theories have been advanced as to the conditions found in acute toxæmia. A toxin of protein origin has been held accountable. Again, an increase in the acidity of the blood, due to the production of butyric and kindred acids by the bacteria. A later suggestion by Wright is that the antitryptic power of the blood is reduced; this allows the trypsin to prepare a suitable medium for the growth of the bacteria in the blood itself and the patient is overwhelmed by an acute invasion of the actual organisms. The subject is much too large to enter into in a paper like this. I merely indicate it to show the sort of prob-

lems that the chemist is asked to solve in pathological or physiological chemistry.

Take the question of toxins. In a rabbit of 2 kilos. weight there is, say, 100 c.c. of blood. Such a rabbit can stand without inconvenience, say, for a very safe estimate, 20 c.c. Eusol intravenously; this contains 0.05 gm. HClO; obviously 0.05 gm. of hypochlorous acid in 100 c.c. of blood can have no possible action as a direct antiseptic. On the other hand, ricin, a vegetable protein poison extracted from castor oil beans, very closely resembling the bacterial toxins, when administered intravenously to a 2-kilogram rabbit in a dose of 0.001 mgrm., kills the animal. A very small amount of hypochlorous acid would suffice to neutralize this dose, if it could reach it.

Hitherto the treatment of conditions due to organic toxins has been based on the conception of a specific antidote; for example, take diphtheria. The method of treating the disease is to inject into the patient the serum of an animal which has been rendered highly immune to the diphtheria toxin. This serum has the power of neutralizing the toxin, but it is a specific power; it cannot neutralize the toxin produced by other organisms, e.g., tetanus. The interest of the method of treatment by intravenous injection of hypochlorous acid lies in the fact that we are able to introduce into the blood a considerable quantity of a strong chemical reagent which will act in a general and not a specific manner.

The chemical reaction between hypochlorous acid and blood is naturally very complex. When hypochlorous acid or hypochlorites act on proteins, the first products are chloramines. In these compounds, which have been studied by Chattaway, Langheld and later by Dakin, chlorine displaces the hydrogen attached to the nitrogen, giving compounds containing the group NCl. These substances give the reactions for free chlorine and are themselves antiseptics of considerable value. As they are formed in the wound or in the blood stream in intravenous injection, and may continue to exist as such for some time, they may prove to have an important bearing on the reactions of the body. They ultimately break down to aldehydes, nitriles, carbon dioxide, ammonia, etc. Work on these compounds as antiseptics has been carried out by H. D. Dakin¹² and others working in Professor Cohen's laboratory at Leeds, and two chloramine antiseptics have been prepared and are now in extensive use. They are known as chloramine T, which is *p*-toluene sulphochloramide, $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NCl}$, and dichloramine T, toluene-*p*-sulphodichloramine, $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NCl}_2$. The former is soluble in water and is used in a strength of 0.5%. The dichloramine is insoluble but dissolves in eucalyptol, which is then diluted with paraffin oil.

In the exigencies of war surgery a large variety of antiseptics, including several synthetic dyes, have been tested, but the general conclusion seems to be that hypochlorous acid, one of the oldest antiseptics, still remains the most reliable for general wound treatment.

In Eusol the full value of hypochlorous acid is available without the drawbacks inherent in the earlier solutions containing this potent reagent.

Some Needed Reforms in Commercial Enlarging Lanterns

In our idea the enlarging lantern should be constructed of metal and asbestos as far as possible. Wood is bulky, liable to warp and burn, and expensive to work. One can make stampings which require little finishing, and an asbestos lining is fireproof, non-conductive of heat, and a protection against short circuiting with electric lighting. The lamp house, as the cinematographer terms it, may conveniently be of cylindrical form, as in one of the American models, the tube being exactly the diameter of the condenser. This is provided with the necessary ventilating apertures and a bed on which the small half-watt lamp can be moved to and fro. The stage to receive the negative should be capable of adjustment so that thick or thin carriers could be used at will. This would allow an arrangement for tilting the negative to be incorporated in the carrier. It would also allow of a small negative being brought further away from the condenser so that it received a greater quantity of light than if it were placed in the usual position. In the case of large lanterns, it is desirable to have smaller condensers interchangeable with the full-sized ones. It is much more convenient to enlarge or reduce from quarter-plate negatives with a 6-inch condenser and appropriate lens than to use an 8-inch diameter for this size.

¹²Dakin and others. Proc. Roy. Soc., 1916, B 89, 232 and B. M. J., 1917, 1, 865.

For clinical trials with Eusol see Lancet., Feb. 5 and 12, 1916.

The arrangement of nearly all the focussing devices is wrong. We have tables of conjugate foci giving distances between lens and paper and lens and negative, and we try to put them into practice by moving the lens instead of the negative. The new enlarger must have an adjustment by which after setting the distance between lens and paper we can move the condenser, negative and light (all together) to obtain a sharp image. With existing patterns with their wooden beds and badly fitting grooves this would be difficult, but with a well-made metal bed it would be quite easy. The best way of effecting this would be to have the whole apparatus on a gantry or base (the lens-board, condenser, and lamp-house being capable of independent motions thereon). The front portion carrying the lens should be fitted with an efficient clamp, so that it would not be disturbed when the negative and condenser were moved to and fro for focussing. It would be an improvement if the negative carrier were detached from the condenser frame, a few folds of bellows intervening; this would allow a small negative to be brought forward so as to receive nearly the whole of the cone of rays from the condenser.

Another point which has been overlooked by nearly all makers is the provision of some means of bringing any part of a large negative opposite the center of the condenser. This was done some years ago by the London Stereoscopic Company, who issued a book-form carrier in which the negative was held by friction between two frames hinged together. In the quarter-plate size any portion of a whole-plate could be accurately squared-up opposite the center of the condenser. As it is, makers give a little rise and fall, though much more sideways movement. It would seem that they regard these adjustments as intended to move the projected image in the easel—not their only purpose. In any case the slot in which the negative carrier slides should be open at the top and have sufficient depth at the bottom to allow the center of a 12 x 10 negative to be placed opposite the center of a 5½-in. condenser. This is frequently required when a single figure has to be enlarged from the center of a group.

The length of the bellows is another matter which is not generally considered as closely as it should be. Nowadays enlarging lanterns are very commonly used for reducing as well as for the purpose they are primarily intended for, and it is very necessary that sufficient length of bellows should be provided for this purpose. We have adapted an ordinary cantilever pattern by making an extension cone to fit in place of the lens panel, thus obtaining an extra draw of twelve inches, but this would be much better done by providing a longer bellows in the first place.

To equalize the light and to soften it so that retouching marks and scratches do not show on the print it is very desirable that arrangement should be made to interpose a piece of very fine ground glass between the lamp and the condenser. It serves as well to destroy the image of the filament or incandescent mantle so often evident when the light is in its best position. Quite a small piece placed close to the light is all that is necessary. When ground glass is used in this way the action of the diaphragm in reducing the amount of light transmitted comes into play. The area of the illuminant is increased, the ground glass itself being practically the source of light as far as the optical system is concerned. Hence the cone of rays from the condenser will not pass through a comparatively small aperture, but requires a large one if short exposures are necessary. From actual trial with a small arc lamp it was found that the entire cone of rays emerging from the condenser passed through the condensing lens at an aperture of *f*/16, but when a ground glass was interposed a perceptible diminution of light was apparent at about *f*/10. Trial exposures then showed that with apertures up to *f*/45 the giving of the standard increase of time to each yielded practically equal results, but with additional contrast, as might be expected as with ordinary camera exposures.—*British Jour. of Photog.*

Revenue by Thawing Frozen Water Pipes

OWING to the extremely cold weather which has recently been experienced in Binghamton (N. Y.) and vicinity, there have been a great many applications made to the Binghamton Light, Heat & Power Company for thawing out frozen water pipes. During the week, January 5th to 12th, there were 80 requests for this class of work. The company's methods of accomplishing these thaw-outs have been very successful and it is a source of considerable revenue. The minimum charge for the work is \$10 per service, to which is added \$1 for each mile that the customer is from the stock room, \$1 for each 100 feet that it is necessary to run service wires, and \$1 for each half-inch increase in size of pipe over 1½ inches. The average return from thawing a pipe is approximately \$13, which is about one-quarter of what it would cost to do this work by other methods.—*Electrical Review.*

⁵Miles. *Edin. Med. J.*, Feb., 1916.

⁶Fraser. *B. M. J.*, Oct. 9th, 1915. *Ed. Med. Journal*, March, 1916.

⁷Sherman. Hypochlorite Solutions for Wound Treatment. *B. M. J.*, 1916, 2, 621.

⁸Lorrain Smith, Ritchie, and Rettle. *B. M. J.*, 1915, 2, p. 716.

⁹Fraser and Bates. *B. M. J.*, 1916, 1, 83.

¹⁰Sir H. Waterhouse and others. *B. M. J.*, 1917, 2, 441.

¹¹Lorrain Smith, Ritchie, and Rettle. *Ed. Med. J.*, Sept., 1917.