THE GERMICIDAL VALUE OF TRIKRESOL.

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Recently a new competitor has appeared to contest the palm with the older germicides. From pre-bacterial days, when Lister first used carbolic acid for antiseptic purposes, basing his action upon Lemaire's discovery that it would prevent fermentation in fluids capable of undergoing that change, down to the present day, this important derivative of coal tar has commanded a wide employment in surgical and sanitary work.

Until 1881, when, influenced by Koch's experiments, bichloride of mercury was brought so prominently to the attention of the profession, carbolic acid had been almost the surgeon's sole reliance in combatting suppurative processes. Henceforth the field was to be equally shared by the mercurial salt, or perhaps it would be more correct to say that carbolic acid was to be relegated to a secondary position in antiseptic work.

But as time passed and observations multiplied, objections were raised against both of these agents. I need not occupy your time with mention of their disadvantages and dangers; suffice it to say that out of these, and out of a wider knowledge of bacteriology, grew aseptic surgery. Unfortunately, however, septic processes still occur, and infected wounds still present themselves for treatment, so that we yet have need of a germicide.

Partly owing to the desire for a safer and more efficient antiseptic for general surgical work, and partly to the pecuniary reward that would attach to the manufacture of an agent which would, at the same time, be applicable to sanitary disinfection, strenuous and unceasing efforts were put forth to discover a body that would satisfy both surgeon and sanitarian.

In 1886, Hueppe presented the merits of "Aseptol," a body which had been known to chemists since 1841 as orthophenol-sulphonic acid, $C_6 H_4 HSO_3 OH$, formed when phenol is dissolved in strong sulphuric acid, and appearing as a syrupy, brownish liquid, having the odor of carbolic acid. Its easy solubility in water and non-irri-

tating qualities when brought in contact with the skin, up to 10 per cent solutions, gave it, in this respect, an advantage over carbolic acid. Hueppe's experiments proved that exposure to 10 per cent solution for thirty minutes and upwards sufficed to kill anthrax spores; but as a 5 per cent solution required twenty-four hours to kill staphylococcus aureus, its action could hardly be called satisfactory.

The following year (1887) Creolin was introduced by the manufacturing chemist. This emulsion of tar oil in resin soaps, familiar to all, was carefully investigated by Esmarch, Van Ermengen, Wehl, Henle, and others, and proved to be possessed of decided germicidal power, being in some respects superior to carbolic acid.

Its turbidity when mixed with water, the slipperiness imparted to hands and instruments, together with the inconstancy of the preparation, were obstacles to its use in everyday surgical work.

It is worth noting here that as the result of careful experimentation, Henle made the observation that both Kresol and Phenol dissolve very well in soap solutions, and concluded that the germicidal value of Creolin was due to some body contained in the tar oil, of which it is made, and which body stands very near to Kresol.

In 1889 Lysol, made by combination of tar oil with strong potash soaps, was put forward as an efficient disinfectant, having this advantage over Creolin that, whereas the latter was a solution of soap in tar oil, the former was said to be a solution of tar oil in soap; and having the further advantage that when mixed with water it formed clear solutions.

Engler's and Dieckhoff's investigations show that the real significance of a turbid emulsion being formed in the one case with Creolin, and a clear solution in the other case with Lysol, upon the addition of water, is due to the fact that the tar oil out of which the former is manufactured contains but little phenol and considerable insoluble hydrocarbons, whereas that used in the preparation of Lysol contains much phenol and only a small proportion of such hydrocarbons. Both of these mercantile preparations possess valuable qualities. They have been found suitable for vaginal irrigation, and particularly good for the cleansing of hands and greasy surfaces of the body; but for the reasons mentioned heretofore they have not met the demands of daily operative work.

In the investigation of Creolin a valuable point was brought

out; for, inasmuch as this agent contained so little phenol and yet exhibited a high germicidal power (staphylococcus aureus being killed in a half minute by a 5 per cent solution), attention was drawn to the insoluble hydrocarbons, the homologues of phenol, contained in the tar oil. I think that to Laplace, of New Orleans, should be given much credit for the work which he did bearing directly upon this matter. Having found that the addition of acetic acid to solution of bicloride of mercury prevented the formation of insoluble albuminates when brought in contact with fluids containing albumen, and thus increased its germicidal action; he next, in 1888, while working in the Hygienic Institute in Berlin, tried the effect of mixing crude carbolic acid and concentrated sulphuric acid, and found that when mixed in equal parts he had obtained a compound which was easily soluble in water, and which was possessed of remarkable germicidal power. A 4 per cent solution in water killed anthrax spores in forty-eight hours, while a 2 per cent solution brought about the same result in seventy-two hours; whereas a 2 per cent solution of carbolic acid or Creolin was without influence. It seems to me that Laplace here took the first step in the evolution, if I may so express it, of the agent which is to-day attracting so much attention abroad as a germicide.

The following year Frankel published an exhaustive review of Laplace's work. He ascertained that by keeping the ingredients at a reduced temperature while undergoing preparation the germicidal value of the mixture was better preserved. Thus prepared, he found that, whereas a 5 per cent watery solution of pure sulphuric acid required twelve days to destroy the vitality of anthrax spores, and a 5 per cent solution of pure carbolic acid fifty-three days, a 5 per cent aqueous solution of the crude carbolic and sulphuric acids killed these spores in less than twenty-four hours; a 4 per cent solution in two days, and a 2 per cent solution in eighteen days. The apparent discrepancy between Laplace's and Frankel's results, the latter explains by the statement that he used anthrax spores which were possessed of "the highest degree of resistance." He thus confirmed the marked superiority of the above mixture over solutions of pure carbolic acid. Frankel next made a mixture of pure carbolic acid and sulphuric acid, and found that solutions of the mixture thus obtained were much inferior in germicidal action to the mixture of

crude carbolic and sulphuric acids. Since this is the case, it would appear that the almost insoluble crude carbolic acid must contain some substance of marked germicidal power which is brought into existence by the addition of sulphuric acid, and is thereby made soluble in water. In order to determine just what this body is, Frankel subjected crude carbolic acid to fractional distillation, and found that the portion distilling over between 185 deg. C. and 205 deg. C. (which constituted one-half of the total distillate) contained the important germicidal body; for if he mixed this part of the distillate with sulphuric acid, the mixture possessed the same great germicidal value. Now since it is known that the boiling point of the different isomeric Kresols lies between 188 deg. C. and 201 deg. C., it is quite probable that this body is one of the Kresols. I will not detain you further with Frankel's experiment than to say that he proved conclusively that the body evolved and brought into solution by the mixture of crude carbolic acid and sulphuric acid, upon which its most remarkable germicidal value depends, is Kresol.

Careful experiments by others have also demonstrated that the valuable antiseptic properties of Creolin and Lysol are due to the Kresol contained in them, and which is in small quantity brought into solution by the resin and potash soap entering into their composition.

Arising from the important work of Laplace and Frankel, a number of investigations have been carried on in Germany, both by bacteriologists and chemists, and a rich literature has sprung up, attendant upon the study of the higher homologues of carbolic acid. New combinations, such as Solveol and Solutol ("neutral watery solutions of Kresol," as Hueppe designates them), made by bringing Kresol into solution by means of sodium cresotate; Lysolum Purum, a solution of Kresol in potash soap, and, lastly, Saprol made by combining crude carbolic acid with petroleum, and whose virtues depend upon its contained Kresol.

What are the Kresols? They are the next higher homologues of Phenol, and differ from it by having one atom of hydrogen replaced by the methyl-group CH_3. Thus, if we represent carbolic acid by the formula $C_6 H_5 OH$, Kresol would be represented by the formula $C_6 H_4 CH_3 OH$.

There are three of these bodies, known as ortho-, para- and meta-kresol. Orthokresol and parakresol are both crystalline bodies, the former having pale reddish, the latter light yellow crystals.

Metakresol is a colorless, thickish fluid, whose boiling point is about 201 deg. C. Since the boiling point of these three Kresols lies very near to each other, viz., orthokresol 188 deg., parakresol 198 deg., metakresol 201 deg., it is a somewhat difficult matter to separate them in a pure state. Heretofore they have been prepared by the action of nitric acid on Toluidin; but recently quite a step forward has been made in their chemical technique, and they are now manufactured in a pure state from coal tar, the three being presented together and happily named Trikresol. This is a white liquid, of a creosote-like odor, having a specific gravity of 1.042-1.049, and is soluble in water to the extent of 2.55 per cent, or say 1 part in forty.

Although possessing this limited solubility in water, Gruber's investigations prove that it is no longer necessary to resort to combinations of Kresol with other bodies in order to increase its solubility, since a 1 per cent solution possesses prompt and marked disinfectant qualities. Now what constitutes, for surgical purposes, an efficient germicide? Shall we accept Koch's standard, and demand that it shall be able to destroy the vitality of anthrax spores within a few minutes? Later experiments, more carefully conducted, prove conclusively that not even bichloride of mercury will do this, I, therefore, think that there is much sound sense in Gruber's remark that it is no longer necessary to make the destruction of anthrax spores within a short time the test of the germicidal value of any agent. What we are really meeting in everyday practice are the non-spore-bearing forms of organisms. If a germicide destroys the pyogenic cocci with certainty by means of short contact, this stamps it, for surgeons and gynaecologists, as a good disinfectant.

Gruber's experiments show that 1 per cent aquaeous solution of the Kresols kills staphylococcus pyogenes aureus with certainty in half a minute, while ½ per cent solutions destroy the same coccus in 10 to 12 minutes.

My own investigations, begun at the suggestion of Surgeon General Sternberg, are, as yet, unfinished, and have been confined to the germicidal action of Trikresol on staphylococcus pyogenes aureus (generally conceded to be the most resistant of the pus cocci), streptococcus pyogenes, bacillus pyocyanus, and the bacillus diphtheriae. Although its action towards the destruction of the Klebs-Loffler bacillus of diphtheria is prompt and pronounced, since the treatment of this disease does not concern us in our capacity as military surgeons, further reference to this organism will be omitted.

The method in testing the agent was that advised by Sternberg, viz., to mix equal parts of a 24-hour old culture of a given organism in sterilized bouillon and of the solution of Trikresol, so as to obtain the proportion desired. In this method, since neither is in preponderance, both micro-organism and agent have a good opportunity to exhibit their capacity for or against a further continuance of vitality.

At intervals of thirty seconds an oese of the mixture was transferred to 5 c. c. of bouillon, and further development watched for a period of two weeks, the tubes being kept at a temperature of 37 deg. C.

Thus tested, I find that one-half per cent solution of Trikresol requires from eight to twenty minutes' contact to destroy the vitality of staphylococcus aureus, while 1 per cent solution kills the same coccus within thirty seconds. After numerous experiments I have never been able to obtain any growth after this interval of exposure to a 1 per cent solution. One-third per cent does not kill in two hours' exposure; 1-800 restrains the development of this coccus. As regards the streptococcus erysipelatos, I find that one-half per cent solution of Trikresol kills it in thirty seconds; 1-800 restrains its development. Bacillus pyocyanus requires the contact of one-half per cent solution for one minute and a half; 1 per cent kills this bacillus in thirty seconds; 1-800 restrains the development of this organism.

One advantage which the Kresols are said to possess is that the presence of albumen in the fluids to be disinfected does not interfere, to a marked extent, with their germicidal action. This is of very great importance, if true. I find that by mixing equal parts of a culture in blood serum of the pathogenic bacteria above mentioned in a solution of Trikresol, so as to give a 1 per cent solution, when mixed, that while a contact of thirty seconds serves to destroy the green pus bacillus, one minute and a half is required to kill the staphylococci and streptococci.

So that, so far as my own experiments have gone, it appears that 1 per cent aqueous solution of Trikresol is, even in the presence of fluids rich in albumen, sufficient for the prompt and certain destruction of the pathogenic bacteria ordinarily met with by the surgeon.

Although it has been stated by several writers that its poisonous qualities are less than those of carbolic acid, I find that recent experiments by Charteris would seem to show, that as far as guinea pigs are concerned, the difference between the fatal dose of Trikresol and carbolic acid is very slight. While a full-grown animal survives the hypodermic injection of either one of these in 7 minim doses, 10

minims of either agent brings about speedy death. But it must be borne in mind, in comparing the poisonous qualities of carbolic acid and Trikresol, that as 1 per cent solution of the latter accomplishes the same results as 4 per cent or 5 per cent solutions of the former, the danger of poisoning is necessarily reduced four or five fold.

Solutions of Trikresol are always clear, and, as used by me, do not impart that disagreeable feeling of numbness to the fingers, such as carbolic acid gives. Sprayed upon the tongue or fauces 1 per cent solution imparts a slight sensation of burning, which is quickly followed by a sense of slight numbness. One-half per cent solution does not excite any disagreeable sensation in my own case, when applied to mucous membrane of throat or nose.

I have thus tried to place before you briefly the merits of Trikresol. Its virtues have been confirmed by numerous foreign observers, who strongly urge its great importance as a germicide. I do not for one moment lose sight of the fact that the work done in the laboratory must be supplemented and put to the final test by the active surgeon and physician. It is this reason, and because of the prominence now given Kresol abroad, especially in Germany, coupled with the almost entire lack of any reference to it in English medical literature, that has led me to bring it to the attention of this Association. To its marked powers as a germicide, both in watery and albuminous fluids, I invite your earnest attention.

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