

A few experiments showed that the ammonia fraction was entirely responsible for the symptoms produced, and that pure ammonium salts, in dose and concentration equivalent to those of the ammonium salts in the "toxin," produced all the effects described, both local and general, in perfectly characteristic manner. Young guinea-pigs showed, in proportion to their weight, the same excessive sensitiveness to the general, convulsant action of ammonium salts as to those of the toxic culture-filtrate. Neither the organic bases, in the proportion present, nor the fatty acids contributed materially to the effect.

There seems, then, to be no ground for supposing that the bacillus of malignant oedema, in an artificial culture of the type described, produces anything in the nature of a specific toxin. The production by it of a toxic solution from meat depends on its intense proteoclastic and desaminating action. The proteins are rapidly broken down to amino-acids, and from these the amino-groupings are then split off, yielding ammonium salts of fatty acids, which accumulate in surprising concentration. To these must be attributed at least the greater part of the acute symptoms produced by the culture-filtrate in the guinea-pig; though doubtless intermediate products of proteolysis may play some part, especially in the delayed death which sometimes follows recovery from the immediate acute symptoms.

The chief interest of the observation seems to us to be the hint it furnishes as to one of the factors favouring spread of infection with the bacillus, in the tissues of an animal in which it has once obtained a hold. It is well known that with washed spores, or even with a broth culture of this organism, it is practically impossible to produce an experimental infection. Some local tissue injury is needed to give the infection a chance of success. This may be mechanical injury, as by contusion of tissue, or irritation by soil particles; or chemical injury, as by lactic or acetic acid. Among such chemical injuries we may now, with some reason, include the effect of the toxic juice formed by the bacillus from meat, which is essentially that of a strong solution of ammonium salts. Given injured tissues in which the growth may start, it is evident that the localized production of ammonium salts will soon be sufficient to create in the neighbouring tissues conditions favouring the spread of the growth, which may then go on indefinitely.

As to how far the production and absorption of ammonium salts, from a large area of infected tissue, may play a part in the general symptoms attending such an infection, we are not in a position to express any opinion. Nor have we studied the production of ammonia in culture by other members of the group.

We hope that these points may receive attention from those who are studying the effects of this group of organisms in the laboratory or at the bedside, and that this publication of observations, so unexpectedly simple in their outcome, may at least save others the trouble of a similar investigation. Our conclusion should, further, make clear the futility of attempting to obtain an antitoxin to the products of the organism with which our observations deal.

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THE ANTISEPTIC ACTION OF HYPOCHLORITES:

THE ANCIENT HISTORY OF THE "NEW ANTISEPTIC."

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THE "new antiseptic" announced in the *Times* of August 8th, and subsequently by many other newspapers, was discovered in 1788 by the French chemist, Berthollet.¹ He obtained a liquid with bleaching and disinfecting properties by the action of chlorine upon aqueous alkalis. The composition of the mixture was obscure, but Berthollet presumed that additive compounds were formed between the halogen and alkali—for example, Na_2OCl_2 .

Berzelius in 1808 expressed the view that the product formed was a mixture of a salt of an unknown acid of chlorine with sodium chloride. The discovery of this acid

—hypochlorous acid—in 1834 by Balard² definitely settled the composition of Berthollet's fluid as a mixture of sodium chloride and sodium hypochlorite.

Four years after Berthollet's discovery—that is to say, in 1792—the corresponding potassium salts were made commercially by Percy at the Javel works near Paris by passing chlorine into crude potashes. The product was sold as eau de Javel,* and its use as a disinfectant was advocated by Berthollet and by Guyton de Morveau.

In 1820 Labarraque³ prepared a fluid similar to Berthollet's by the action of chlorine (1 mol.) on an aqueous solution of sodium carbonate (2 mols.). This preparation containing much free alkali became known as "Liquor de Labarraque," or "Labarraque's disinfecting fluid." It is related that Labarraque, who was pharmacist first to the Emperor and subsequently to Louis XVIII, achieved great renown on the death of the latter monarch, for, thanks to the disinfecting and deodorizing value of his "liqueur," he was able to proceed with the embalming of the royal body, which was so profoundly decomposed that no one was able to approach it until after the application of the hypochlorite solution.

At a later date solutions of the hypochlorites of sodium and potassium were largely replaced by the more stable solid "chloride of lime," a combination of calcium chloride and calcium hypochlorite. It is interesting to note that it was with this substance that Semmelweis in 1846 succeeded in eradicating endemic puerperal fever from his clinic.

Subsequently the liquor de Labarraque and eau de Javel, as well as the liq. sodae chlorinatae of the *Pharmacopoeias*, were generally prepared by the decomposition of chloride of lime with the carbonates or sulphates of the alkali metals, and this simple process has been the subject of innumerable patents applied for long after the process was well established in common practice.⁴

In 1859 Charles Watt discovered that sodium hypochlorite could be formed by the electrolysis of sodium chloride solution, and a similar electrolytic process was patented by Andreoli in 1890. Since then scores of different modifications for the electrolytic preparation of hypochlorites have been advocated.

Other hypochlorite preparations, such as "extrait eau de Javel," "esprit de Javel," "essence de Boulogne," "chlorozone," "hermitine," "chloros," etc., need not be referred to in detail, since they represent hypochlorite preparations of varying purity and stability.

Meanwhile the hypochlorites, and by implication hypochlorous acid—for the latter is liberated from its salts by the carbon dioxide of the atmosphere—were finding an ever-extending application as general disinfectants. They were also employed for the sterilization of polluted supplies of potable water, and to a lesser extent for surgical dressings and for oral antiseptics. I am informed that "liquor sodae chlorinatae" has been used at St. Thomas's Hospital as a dressing for amputation stumps as long as sixty years ago. In more recent times weak hypochlorite solutions have been used with more or less success for removing sloughs and for controlling the smell of offensive wounds. As a skin disinfectant for use in pathological laboratories hypochlorite solutions have been used by Professor Delépine for a generation past.

The great drawback to the more general use of hypochlorites as antiseptics has been the strongly irritating character of the commercial solutions. In the early part of the present war some French surgeons made use of the ordinary "eau de Javel," but there were many accidents owing to its caustic action. It was for this reason, therefore, that it seemed worth while to try and obtain a solution of hypochlorite with fewer objectionable qualities. This was done in January of the present year, and after the solution had been in constant use for many months a short communication written by me was presented at the French Academy of Sciences. The essential parts of the communication are the following:

"*Parmi les antiseptiques qui ont déjà été étudiés dans le traitement des plaies infectées, les hypochlorites surtout remplissent les conditions qui viennent d'être énumérées. Mais malheureusement les hypochlorites du commerce ont une composition très inconstante et contiennent généralement de l'alcali libre ou du chlore libre.*

* At the present time in France the term "eau de Javel" refers usually to sodium hypochlorite solution and not the potassium salt.

De telles solutions sont irritantes. Quand on s'en sert, même sous une concentration modérée, elles peuvent produire des résultats peu favorables. Il était donc utile de trouver le moyen de préparer un hypochlorite de composition constante qui possède une grande activité bactéricide et une faible action toxique et irritante sur les tissus. Ce résultat a été obtenu par la méthode suivante :

The method of preparation already published in this JOURNAL⁵ is then described. The principle of the process being the decomposition of chloride of lime with a slight excess of sodium carbonate solution, filtering off the solution of sodium hypochlorite, which is then neutralized with boric acid in such a fashion that the resulting solution reacts acid to phenolphthalein but alkaline to litmus. "On a trouvé que cette solution est un antiseptique très utile dans le traitement des plaies infectées, lorsqu'elle est appliquée suivant la méthode étudiée et employée par le Dr. Carrel."

It will be seen that no suggestion of a claim for novelty in the employment of hypochlorites or hypochlorous acid is made, but distinctly the reverse, as indicated in the first sentence quoted above.

Following this communication of mine to the Academy, the *Times* on August 8th, 1915, announced in the most sensational fashion the discovery of the "new antiseptic" just 127 years after the preparation of sodium hypochlorite by Berthollet.

It might have been thought and hoped that the absurd and extravagant statements made in the lay press would have sunk into oblivion, but this was not the case. The press which had directed so much unwelcome attention to my communication made in Paris had ignored a valuable paper published shortly before by Lorrain Smith and his colleagues,⁶ which also dealt with the antiseptic action of hypochlorites. The *Times* now published a letter from Professor Harvey Littlejohn, Dean of the Medical Faculty of the University of Edinburgh, who, without waiting to read my communication in print, stated that "it was only due to certain members of the university to state that five months ago they recommended for surgical purposes the employment of what appears to be the same antiseptic." The surmise as regards identity of composition was quite incorrect save for the fact that the hundred years old hypochlorites and boric acid were constituents of both solutions. The *Lancet* apparently obtained its information from the daily papers and devoted more than a column of space to the new antiseptic.⁷ Almost the whole of the statements made relative to the solution referred to in the Paris communication are incorrect and misleading. The article ended with the statement that the result of the Edinburgh workers was to confirm the conclusion of various investigators that hypochlorous acid is the most powerful antiseptic known! It is perhaps worth pointing out that such a statement without qualification as to the conditions under which the antiseptic acts is devoid of meaning. Disinfection is a chemical reaction in which the reactive agent acts not only on bacteria but upon the media in which they are found. A large number of antiseptics are known which will kill many micro-organisms suspended in water or blood serum at much lower concentration than will hypochlorites and hypochlorous acid. No statement of the relative power of antiseptics is possible except under absolutely comparable conditions. An antiseptic which shows a high relative activity under one set of conditions will often show a low one when conditions are changed.

In France the interesting results of Vincent and Lumière on the use of hypochlorites for surgical dressings were referred to in the lay press, while, as a climax, the announcement was solemnly made in the *New York Times* by Dr. Jenkins, former Medical Officer of Health for New York City, that it was Mr. A. E. Wolff of that city who discovered, some twenty years ago, the application of hypochlorites as deodorants, antiseptics, and germicides.

It would seem as if the time was fitting for a statement to the effect that what we have all been striving for is to find the best means of preparing, preserving, and applying

the powerful antiseptics, hypochlorites and hypochlorous acid, the main properties of which substances were discovered by distinguished French chemists many generations ago.

Lorrain Smith and his co-workers have aimed at a more or less complete liberation of free hypochlorous acid from chloride of lime by the addition of an equal weight of boric acid. Lumière, on the other hand, employed three parts of boric acid to one of chloride of lime with satisfactory results. On the other hand, my own experiments aimed at the preparation of a sodium hypochlorite solution with a low OH ion concentration, sufficiently stable, and containing a balanced mixture of polyborates so that approximate neutrality might be preserved under all circumstances. The amount of free hypochlorous acid in my mixture is much smaller than in Lorrain Smith's or Lumière's preparations. The concentration of available chlorine is less, and it can be more freely and continuously applied.

Recently I have been interested to find that Dr. Heitz-Boyer and the staff of the French hospital ship *Charles Roux* have been making extensive use for surgical purposes of a hypochlorite solution prepared by the electrolysis of sea water in a simple cell using carbon electrodes. The hypochlorite concentration employed varied from 2 to 4 grams of hypochlorite per litre, the lower dilution being used for constant irrigation. The electrolytic hypochlorite is peculiarly unstable.

When suitably applied there seems no doubt that all of these hypochlorite preparations are of genuine value in the treatment of infected wounds.

There is one point concerning the mode of action of hypochlorites that I would like to refer to before closing. It has been repeatedly stated that the antiseptic action of hypochlorous acid is due to its decomposition in the presence of organic matter with liberation of oxygen. I have been unable to find any evidence to support this statement. If it were true that the antiseptic action of hypochlorous acid was due to the liberation of oxygen, it is surprising that many other substances capable of furnishing nascent oxygen should have an antiseptic action far inferior to that of the hypochlorites. Moreover, I know of no evidence pointing to an accelerated liberation of oxygen from hypochlorous acid in the presence of organic matter. The ordinary decomposition of hypochlorous acid with liberation of oxygen is a relatively slow reaction. Furthermore, when strong hypochlorite solutions are added to animal tissues, an evolution of chlorine rather than oxygen occurs.

It appears that when hypochlorous acid or hypochlorites act upon organic matter of bacterial or other origin some of the (NH) groups of the proteins are converted into (NCl) groups. The products thus formed—belonging to the group of chloramines—I have found to possess approximately the same antiseptic action as the original hypochlorite, and it appears more probable that the antiseptic action of the hypochlorites is conditioned by the formation of these chloramines rather than by any decomposition with liberation of oxygen. It should be noted that the hypochlorites act upon free ammonia to yield the simplest chloramine NH_2Cl , as first shown by Raschig. The probable formation of this substance during the sterilization of sewage with hypochlorite has already been indicated by Rideal and others.⁸ The chloramines formed from proteins when wounds are treated with hypochlorites are naturally of a much more complicated character.

REFERENCES.

- ¹ *Statique chimique*, 2, p. 783. ² *Annales de chimie*, 57, p. 225. ³ *Jour. chimie médicale*, Paris, 2, p. 165. ⁴ Cf. *Conteille's French Patents of 1873*. ⁵ *BRITISH MEDICAL JOURNAL*, August 28th, 1915. ⁶ *Ibid.*, July 24th, 1915, p. 129. ⁷ *Lancet*, August 14th, 1915, p. 348. ⁸ *Jour. Roy. San. Inst.*, 1910, xxxi, p. 34.

DR. JOSEPH GOLDBERGER, of the United States Public Health Service, who has been investigating the cause of pellagra, which caused the death of more than 11,000 persons in Mississippi alone last year, has, says the *Medical Record*, been helped in his work by prisoners in the prisons of that State who have voluntarily submitted to experiments. Out of eleven prisoners who were observed, six have developed the disease. The men have all been pardoned, and will be released as soon as a course of treatment on the prison farm has restored them to health.

* As a matter of fact, my communication to the Academy did contain references to some genuinely new antiseptics of the chloramine type, but no comment on these substances was made in the lay press.