Oil.	Refractive index at 20° C.	Optical rotation in 100 mm. tube at 25° C.
Nutmeg	1.4837	+12° to +30°
Origanum	1.4841	—15° 36′
Pennyroyal	1.4821	+18° to +22°
Peppermint	1.4636	—23° to —33°
Pine Needles (Siberian)	1.4729	—4.5° to —9°
Sandalwood	1.5061	—15° to —20°
Sassafras (Artificial)	1.5273	.....
Sassafras (Natural)	1.5299	+3° to +4°
Sassafras (Safrol)	1.4684	.....
Spearmint	1.4894	—38° to —55°
Spruce	1.4706	—29.27°
Thyme (Red)	1.4925	Slightly levorotatory
Thyme (White)	1.4903	Slightly levorotatory
Wintergreen (Methyl salicylate)	1.5379	.....
Wintergreen (Birch)	1.4971	.....
Wintergreen (Natural)	1.5029	—1.5° (not exceeding)
Wormwood	1.4741	.....

In the determination of adulterations in essential oils the refractive index or the optical rotation, alone, might not be of much value, but taken together with other constants they are often of prime importance.

THE CHLORAMINES:* THEIR PREPARATION AND USES.

BY ISAAC F. HARRIS.

The war in Europe has developed a vast number of new antiseptics and disinfectants during the last few years.

Pressure has been brought to bear upon the chemical profession to create and produce active, efficient, powerful, non-irritating, non-toxic and economical germicides particularly adapted to the sterilization of infected wounds.

To combat the multitudinous infection of war wounds there have arisen:

Antiseptic dyes (malachite green and acriflavine), eupad, eusol, compounds of mercury, silver, iodine, bromine, and, lastly, Dakin's solution and the chloramines.

These latter are the special subject of our consideration here.

In the same manner that the war has forced the development of our industrial life, it has, likewise, stimulated pharmaceutical and chemical growth, especially in their applications to clinical medicine and surgery.

When our war surgeons faced a rampant infection upon a scale hitherto unknown to mankind, they appealed to the chemists to solve this problem.

All of the older and well-known antiseptics failed, in some quality, to fulfil the demands. Salts of mercury were too toxic, phenol was inadequate, compounds and salts of silver were too expensive and too toxic to tissue, formaldehyde was too irritating, while tincture of iodine—anything in alcoholic solution—was too expensive and irritating.

Thus, one by one, they were abandoned.

What was the problem?

*Read before Scientific Section A. Ph. A., New York meeting, 1919.

There was a crying demand for a *water-soluble* disinfectant which could be employed freely as an irrigant for deep wounds.

It must be non-irritating, non-toxic to body tissues, effective in its germicidal properties, economical, available and safe.

Dakin and Carrell solved it at Base Hospital No. 21, Compiegne, France, working under the joint auspices of the French Army and the Rockfeller Institute of New York.

The products are now well-known as Dakin's solution (neutral sodium hypochlorite solution) and the chloramine derivatives of toluene (chloramine-T and dichloramine-T).

All of these depend upon the same principle, namely, the chemical power of chlorine to destroy living organic matter.

In Dakin's solution we have an application of "available chlorine" in an aqueous solution, under precise and standardized conditions.

It has been spoken of as a "glorified" bleaching powder, "refined" and adapted to surgery.

It is standardized to contain 0.46 to 0.50 percent sodium hypochlorite, and to have an exact chemical neutrality, as indicated by phenolphthalein, in strong alcoholic solution.

The great value of Dakin's solution in the treatment of infected wounds is two-fold:

First: The disinfectant value of its "available chlorine."

Second: The *solvent power* upon necrotic tissue, due to the formation of sodium hydroxide as part of its decomposition in the presence of protein matter.

The former accomplishes its extensive and elaborate effects through the preparatory action of the caustic soda, which makes *contact* with the micro-organisms possible.

On the other hand, the action of the *caustic* ("solvent") is limited by the amount of chlorine in the solution and by the amount of necrotic tissue present which causes the double decomposition.

This is an automatic, self-regulating system which is beautiful, both in theory and adaptation.

But, what are the *limitations* of Dakin's solution?

It is unstable in character, transient in value, very intricate in preparation, elaborate in its application and serviceable only in certain types of infection.

The preparation of a precise solution of sodium hypochlorite of exact neutrality, and containing chlorine within the limits prescribed by Dr. Dakin, requires a first-class chemical equipment and the services of one experienced and skilled in this particular work.

Let us face this chemical problem squarely!

The specifications allow a variation of 0.01 percent chlorine only.

If this solution is too high in its content of sodium hypochlorite, it is dangerous in its effect upon tissue.

If too low in strength, it is of less value than described.

Again, adjusting such a solution to an exact neutrality—in an unionized solution—is a test of a high order.

An alkaline Dakin's solution is irritating and hazardous in effect. An acid

hypochlorite does not exist. Experience has shown that such specifications are not carried out in general practice.

The authors recognized this and created chloramine-T and dichloramine-T to make solutions of "available chlorine" more exact in composition and more lasting in effect.

Chloramine-T is a white, crystalline powder, quickly soluble in water to form a clear solution.

It is stable—both in powder and in solution—is non-irritating, non-toxic and highly germicidal.

A 2 percent solution of chloramine-T contains *0.25 percent "available chlorine"* and is chemically neutral.

Dakin's solution, under *optimum and maximum* conditions, contains *0.23 percent "available chlorine."*

The former will keep indefinitely while the latter is suitable for use only for a few days.

A 2 percent solution of chloramine-T is available to everyone, everywhere and requires no skill in preparation.

The advantages to the medical profession of such a portable compound are obvious.

Likewise, it offers to the pharmaceutical profession and dispensing druggists a *safe method* of dealing with the physician and institution.

While a 2 percent solution of chloramine-T will accomplish all that Dakin's solution will and can be employed in the same cases by the same technique, yet it offers the further advantage of application in greater strength or greater dilution, as the profession may require.

The specifications for purity of this compound are that it shall be para-toluene-sodium sulphochloramide, white, crystalline in form, completely soluble in water, and shall contain 12.6 percent of "available chlorine."

Another application of chloramine-T by Dr. Carrel was in the form of a *surgical paste* for dressing of sterile or moderately infected wounds.

This was devised by Dr. Maurice Daufresne and consists of a surgical paste of the "vanishing cream" type, compounded with neutral sodium stearate, carrying 1 percent of the disinfectant, chloramine-T.

While these are the essential features and factors of Dr. Daufresne's wound dressing cream, as employed by Dr. Carrel, it is of the highest importance to prepare it strictly in accord with the advices of the authors. The fineness of subdivision of the particles of insoluble soap control the distribution of the antiseptic, while the high purity of the fatty acid and strict chemical neutrality of the resulting sodium soap—in unionized solution—all contribute toward the permanence of the preparation and to its clinical effects.

When properly prepared and packed in suitable, air-tight, containers, this preparation keeps indefinitely.

Chloramine-T surgical paste is safe in the hands of the dispensing chemist, provided these precautions are strictly adhered to. This description furnishes the essential specifications for its purity.

Much confusion has arisen in the minds of the profession through the variety of chlorinated compounds which have been proposed for disinfectant purposes.

The reason for this has been an attempt to satisfy a variety of demands. The physician must have a choice of disinfectant agents, just as he has a choice in selection of his anesthetic.

Dakin's solution is a vigorous, radical disinfectant.

Chloramine-T is milder in its action, though stable and uniform.

To supply further requirements, *dichloramine-T* and its oil-solvent, *chlorcosane*, were evolved.

Since dichloramine-T contains two chlorine atoms instead of one (as in chloramine-T) it not only carries more chlorine (29.5 percent) but this latter element is less firmly fixed in the molecule.

The result is that it gives it up more readily when in contact with dead organic matter, and is less stable in character.

Dichloramine-T is insoluble in water, which is one of the features intended in its selection.

A *specially-prepared*, "chlorinated" oil (chlorcosane) has been created by Drs. Dakin and Dunham as a bland, neutral carrier of this disinfectant.

Dichloramine-T is always applied to infected areas in chlorcosane solution, which delays the reaction between the aqueous tissues and the disinfectant, thereby prolonging the action of the latter.

This feature of dichloramine-T-oil dressing of wounds is important from the standpoint of renewal of dressings.

Another wide use of the dichloramine-T-oil dressing has been developed at the Pennsylvania Hospital and elsewhere; upon *extensive burns*, where this dressing relieves pain, the disinfectant prevents infection and the dressings are readily removed.

The specifications for the purity of dichloramine-T are that it shall be toluene-para-sulphondichloramine, yellow-white, crystalline or amorphous powder. Its melting point is 80° C, and it should dissolve readily in chloroform or chlorcosane. It should be kept from direct, prolonged sunlight, moisture, organic matter and metals.

In dispensing dichloramine-T from larger containers, unless all these precautions are observed, a decomposition will be set up which will continue, until the whole mass is badly decomposed, with liberation of chlorine, leaving the amide, which is insoluble in chlorcosane.

The selection of a solvent for dichloramine-T has been a problem.

Though it will dissolve in certain other oil solvents, the fact that it has a decomposing action upon the solvents, themselves, must be noted.

Hence *chlorcosane* originated.

When white paraffin wax is melted and treated, white hot, with chlorine gas, it will absorb and combine with the latter to form chlorine derivatives which are very stable. When the paraffin has been thus vigorously treated with chlorine, its affinity or avidity for this halogen is so satisfied that it has very slight decomposing effect upon the dichloramine-T.

Although various oil solvents for dichloramine-T have been suggested—and used to some extent—there is only one which has satisfied the tests and requirements of the Army, the Navy, Red Cross and general practice; that is *chlorcosane*.

It is, furthermore, important to remember that though chlorcosane contains approximately one-third of its weight of chlorine, yet it *has no antiseptic power*, in itself, since this chlorine is combined with the carbon of the molecule and is inactive, stable, *firmly fixed* as in sodium chloride.

The specifications for chlorcosane are that it shall be chlorinated paraffin; a golden yellow, lustrous oil, of sp. gr. about 1.06 (slowly sinks in water at 20° C), tasteless, bland, odorless, neutral and a solvent for dichloramine-T, up to 8 to 10 percent.

In summary, the derivatives of chlorine all have their place. Their very nature demands that they be prepared in condition of high purity, transported and dispensed with precautions, and that the ultimate consumer shall understand their properties.

Many confident pharmacists have attempted to make Dakin's solution by new and self-improved methods. They have combined the chloramines with wool fat, petrolatum, liquid petrolatum, and other soaps than that prescribed by Daufresne. These experiments are futile. Let's adhere strictly to the fundamental requirements of the authors.

The chloramines have found their place in surgery and are now establishing themselves in the institution and household as the best, most highly germicidal and safe disinfectants for general use in combating infection, to-day.

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NEW YORK.

ABSTRACT OF DISCUSSION.

MR. LOWENSTEIN: There are a few points brought out by the speaker in reading this paper with which I don't agree. I would like to have them cleared up if possible. First of all, is he justified in making the statement that it is very difficult to prepare the Dakin's solution so that it is perfectly neutral? My experience has shown that it is the easiest thing in the world, and that anybody with any training can do it. Secondly, the author forgets to mention the fact that Dakin's solution has a property of dissolving necrotic tissue, and this was considered one of its most important properties, while chloramine-T, as far as I know, has not that property; and that is why Dakin's solution is to be preferred to any one of these products. Finally, the objection to Dakin's solution was raised that it is unstable. I wonder whether the author is familiar with Cullen's paper published recently, where he goes into the method of preparing it, and finds it to be perfectly stable; that Dakin's solution is easily prepared, and much more stable than stated, and it is cheaper than the chloramines.

MR. HARRIS: I will not agree that Dakin's solution is superior to all the others on account of its solvent power upon necrotic tissue. I will agree that this solvent power does not exist in the same degree in the other products; the disinfecting power of the other products, however, is greater. This solvent power of the Dakin's solution upon necrotic tissue is admitted. It has solvent power upon wounds; that is well known; and it causes hemorrhages, sometimes. Dakin's solution is a wonderful product, but is not always available. The man in the little town in Kansas or Missouri, and other states of the country, cannot get Dakin's solution, and he cannot make it properly. The chloramines were designed, to a certain extent, to reach the fellow in the part of the country where you cannot get Dakin's solution. Probably you are in a position to get Dakin's solution, properly made, but I know from two or three years' experience, traveling all over the country, that the average man never gets a neutral, fully potent solution of sodium hypochlorite, as prescribed by Dakin. I traveled over the country from coast to coast, calling on large and small pharmacies, in the small towns and in the hospitals, and am convinced that the situation is as described. A very small percentage of the chemists and

practicing pharmacists are able to make it properly. It is not a question of education or mentality, or anything else of that nature; it is a matter of equipment and time. A physician in a small town sends in a prescription for Dakin's solution occasionally, and the pharmacist has not the time nor the equipment to make it right, yet he tries. I can tell you of an able pharmacist, up in New Haven, Conn., one of the best men in the town, who has been dispensing Dakin's solution combined with wool fat and other ingredients incompatible with it. And the doctors get it. This is worse than useless. It is prepared in other places in a similar manner, and such practice is damaging to the success of the great work that Dr. Carrel of the Rockefeller Institute is carrying on. My point is this—that in many parts of the country Dakin's solution cannot be properly made so that the patient suffering from infected wounds can get the benefit of it. Recognizing this situation, physicians are applying some of the more stable and more easily obtained chloramine products. You spoke of the paper written by Dr. Glenn E. Cullen, of the Rockefeller Institute, published in the *Journal of Biological Chemistry*, May 1919. You spoke of his stabilizing sodium hypochlorite solution. It is impossible. I talked it over with him for hours. He cannot make it stable. He has made it a little more stable. They cannot make it stable like chloramine-T. This is one of the advantages of the latter.

MR. HAMILTON: Of course the question of its stability is an important one. But for the purpose of making a Dakin's solution that is a fairly stable compound there are a number of preparations on the market of sodium hypochlorite that are dispensed under other names, containing something like 4 percent of available chlorine. These solutions are made in such a way that they are fairly stable. When the gentleman says that it is impossible to make them stable, that word "stable" ought to be defined, because stability is a question of days or months or years. You do not expect a hypochlorite solution to be stable for years. I have known of some of these solutions that have proved to be stable for a very considerable period of time. I cannot, for the moment, say offhand. I want to ask one or two questions: On the table up there, are there any data on the germicidal value of the solution containing 0.25 percent of chlorine? Also, in the case of this solution of 2 percent chloramine-T, what is the active agent? As I understand it, in Dakin's solution of hypochlorite, oxygen is the disinfecting agent. Is that true in the case of chloramine-T? The speaker referred rather slightingly to mercury because of its being put in the class of a poison. I don't know, but as I understand it, in almost every case the action is that of the protoplasmic poison, and it makes no difference whether it is chlorine, oxygen, mercury, or whatever it may be.

MR. CLARK: From my investigations I believe that the greatest source of trouble in making Dakin's solution has been due to the lack of explicit directions.

MR. MURRAY: The use of chlorinated solutions of various kinds has extended to a considerable number of products, many of which are familiar to you gentlemen present. Some of them are manufactured in this country, and we have the promise that the manufacturers will shortly undertake the making of others.

MR. KEBLER: I would like to inquire whether the gentleman believes that we have had sufficient experience in the use of these products at this time to be certain of their practicability? We have had several new things introduced to us within recent years for which much was claimed, but after experience with them for two or three years we found out that they did not make good; at least they did not make good to the extent claimed for them. I would like to ask the gentleman whether he knows that these goods have been tested to the extent that they will make good or have made good?

MR. HARRIS: You spoke of your own experience in making Dakin's solution, and you state that it is stable. The question of stability, however, is a matter of whether you mean one year, or six months, or what period of time you require it to be stable. I understand that there are on the market, at the present time, various sodium hypochlorite solutions containing about 4 percent available chlorine, which can be diluted down to the required amount of chlorine for Dakin's solution, and then shaken up with boric acid, or with sodium bicarbonate to neutralize it, and thus make an approximate Dakin's solution. That is one of the ways of making Dakin's solution. It is quite all right, but requires an accurate chemical analysis at frequent intervals. Furthermore, the chemical *reaction* must be adjusted with great precision. And, I maintain that testing for neutrality of such an un-ionized solution as sodium hypochlorite, with phenolphthalein, in alcohol, is a test of a high order and requires familiarity with such reactions and

chemical adjustments. On the other hand, when one makes up a 2 percent solution of chloramine-T, it is *neutral* and ready for immediate use, without chemical adjustment. The disinfectant power of Dakin's solution is two-fold: You start with a neutral solution, but when this sodium hypochlorite comes in contact with dead pus cells, blood clots, and such organic matter, the "reactive chlorine" combines with such matter, setting free molecules of hydrogen, which combine with the sodium to form sodium hydroxide in an amount equivalent to the molecules of chlorine used up by the necrotic cells. This automatic formation of caustic soda from neutral Dakin's solution is responsible for the solvent power of this disinfectant. In answer to this second question upon the bactericidal value of this solution (2 percent chloramine-T) mentioned on the chart, it is hard to answer, since its bactericidal value depends upon what is in the solution. It is impracticable to make a general statement concerning it. It depends upon the culture, the bacteria; also upon whether you have a certain amount of tissue to deal with, either blood clots or some other form of tissue that is being treated, which will tend to "use up" the disinfectant. You will find a number of bactericidal tests of the chloramines given in the handbook by Dakin and Dunham. One statement that they make is that a solution of chloramine T, 1 to 1,000,000, will sterilize a suspension of streptococci in water.

MR. BERRY: Mr. Harris has been asked concerning chloramine-T, if he knew whether an absolutely neutral solution is stable. Some manufacturers in making chloramine-T will not make it without having at least four-tenths of 1 percent alkalinity to preserve it. They found that did it best, and in my laboratory I have tried some eight or ten samples. I found that those which were absolutely neutral did decompose in three or four months, very slightly. That is because of the alkalinity not being of the satisfactory strength, to just over the point where it would keep.

MR. WRIGHT: I had some experience several years ago in making Dakin's solution. As I understand it, Dakin's solution is simply a modification of Labarraque's solution which was in the National Formulary. Inasmuch as we have come to learn so much of the value of Dakin's solution, and know its wonderful effects in the war, I make the suggestion that Dakin's solution be included in the National Formulary, with proper directions for preparation. I think that it will be very well for this Section to make the recommendation that it be included in the Pharmacopoeia.

THE CHAIRMAN: Do you make that in the form of a motion?

MR. WRIGHT: Yes.

THE CHAIRMAN: Is there any second to the motion?

MR. COOK: I second that motion, if you will limit it to the N. F. (The motion was put to vote and carried unanimously.)

MR. KEBLER: I would like to ask this question; I want to know whether under these circumstances related concerning this product, that it has been put out on the market, whether it has been out a sufficiently long time to warrant the claims that are made for it.

MR. HARRIS: My answer is, that it does keep. It is neutral. Chloramine-T is a very well-known substance and was used during the war. It was not discovered during the war; it was discovered long before the war. It is a very well-known chemical compound, and is stable. You referred to the keeping of the chloramine solution. You did not find that it kept? Let me tell you what I think happened in your case; your solution did not keep because it was not pure, perhaps. It will not keep unless it is pure. That is true. If they are impure, the chances are that they will keep better if they are alkaline. It is a stable compound. You know the chemistry of it. Kissel was one of the authors referred to by Dakin and Dunham, who described it in 1895. They described it, and endorsed it as a perfectly stable compound. A great deal depends upon how it is handled. If you have cork stoppers, if you don't use distilled water, if your bottles are not thoroughly cleaned—all those things influence the quality of the product. If you use pipe water, or bad distilled water, especially if it is overcharged with acid salts, you will get a decomposition and it will increase. But the chemical compound itself is considered a perfectly stable substance, just like mercuric bichloride. When we speak of dichloramine-T, we qualify it. That is not so stable. We have to describe it with some qualifications.