of the New York Pharmaceutical Association held in Saratoga Springs in June, a committee of ten was appointed to discuss this question of the separation of the sheep from the goats. He thought the proper solution of the question was one that required careful deliberation; that it was well worthy of a further study and moved that the proposal be referred to a sub-committee for consideration during the year, with instructions to report to this body. He again referred to the fact of the appointment of the committee in New York, and thought it quite likely that other committees had been appointed in other states.

Dr. Arny stated the idea of the paper was merely to present the subject that the members might think it over. He referred to the appointment of the committee in New York to look into this particular matter. In conclusion, he wished to say relative to Mr. Apple's criticism, that naturally the requirements of membership were purely tentative; that it was merely the thought he was trying to present, and therefore he would be most happy to go before the committee.

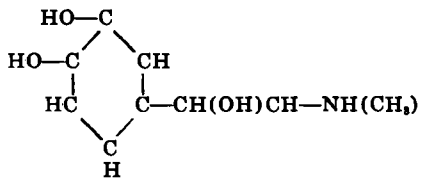
Dr. Apple, replying, said he wished Dr. Arny to understand that his remarks were not criticisms.

THE PHARMACY OF ADRENALIN.

C. P. BECKWITH.

Adrenalin has, to-day, a well-established place in the materia medica. In therapy, its field is large and expanding. Its chemistry and pharmacology have been studied elaborately. Of its pharmacy, however, comparatively little has been written. In dispensing this sensitive substance, there is much opportunity for error. I believe it a moderate estimate that of adrenalin-containing prescriptions met in actual practice, more than half are either ill-written or improperly compounded. In the present paper, it is proposed to discuss briefly the pharmacy of adrenalin, and, particularly, to suggest certain expedients and precautions favoring the conservation of its activity alone and in mixture.

The structural formula, when known, constitutes, perhaps, the most precise possible definition of a pure chemical compound. In the case of adrenalin, the formula has been established, beyond doubt, by both analysis and synthesis; for the sake of precision, therefore, let us define adrenalin as the lævo-rotatory isomer of the formula,



The dextro-rotatory isomer of the same formula, which has been found in the synthetic product only, is probably nearly or quite inert.

While this formula is before us, it is well to observe that the molecule contains groups that characterize it at once as an amine base, an alcohol and a phenol,—an observation that will help to a clearer understanding of its chemical behavior.

Adrenalin occurs naturally in the medulla of the suprarenal gland of warm-blooded animals, including man. Suprarenal glands of oxen, which are most readily obtainable in sufficient amount, supply the adrenalin of commerce. We

have no reason to doubt, however, that the natural substance is the same from whatever animal obtained.

Details of a process, identical in all essential points with that used on the manufacturing scale for the isolation of adrenalin from the gland tissue, may be found in an article by Dr. Takamine in the American Journal of Pharmacy, November, 1901.

Adrenalin of commerce, a nearly white micro-crystalline powder, is substantially pure, containing a very small fraction only of foreign matter. When properly stored, the pure crystals will remain unchanged for many years or perhaps indefinitely, but certain precautions should be observed as to the conditions of storage. Air, ammonia and certain other gases, moisture, strong light and heat, are in different degrees injurious. Under the combined action of air and moisture, adrenalin is decomposed rapidly. It is well, therefore, to store the product away from strong light and heat, in absolutely dry glass bottles or tubes, sealed air-tight. The drying of the container should be very thorough indeed, and, of course, the substance itself should be quite dry. A further precaution, superfluous however in ordinary practice, is to displace the air from the container with a dry inert gas. So protected and hermetically sealed, it is probable that adrenalin would prove absolutely permanent.

The pure substance is slightly soluble in cold water, and to a somewhat greater extent in hot water. Other ordinary simple solvents dissolve it very little, if at all, though aqueous solutions of certain salts have a marked solvent action. For instance, a strong aqueous solution of a borate, dissolves adrenalin abundantly, and borates prevent its precipitation by alkalies from solutions of its salts. Also, a strong aqueous solution of chemically neutral adrenalin chloride, will dissolve an appreciable amount of the adrenalin base.

In virtue of its phenol function, it forms water-soluble compounds with fixed caustic alkalies, but not with their carbonates nor with ammonia. Hence, from strong solutions of most of its salts, while the adrenalin base is partly precipitated by hydroxides or carbonates of strong alkalies, including ammonium, it is re-dissolved by excess of the fixed caustic alkalies only.

None of the solutions mentioned so far, is recommended for use in pharmacy, since in all, the adrenalin is oxidized rapidly on exposure to air.

In virtue of its amine function, adrenalin forms definite salts with the acids, usually very hygroscopic and difficult to preserve in dry form. They are in general very soluble in water and in alcohol, and these solutions may be made sufficiently stable for all ordinary uses. The salts are not very soluble in common simple solvents other than water and alcohol. For most pharmaceutical purposes, therefore, we are limited to the use of the salts of the base, in aqueous or alcoholic solution.

For instance, desiring to make an ointment containing adrenalin, the best practice is to prepare first, a concentrated aqueous solution of the chloride by dissolving adrenalin in the proper quantity of cold, moderately diluted hydrochloric acid, to incorporate the solution with sufficient lanolin, which as you know will take up much water, and to add, finally, whatever other ointment base may be prescribed. In case the prescribed fatty base, is miscible with sufficient alcohol,

it may infrequently be advisable to dissolve the adrenalin in the proper proportion of alcoholic, instead of aqueous, hydrochloric acid.

Very occasionally, ointments, suppositories, bougies, etc., containing adrenalin, are ordered, and the general method for ointments just outlined will suggest how they may be prepared.

Most commonly, however, aqueous solutions are prescribed; in fact commercial solution of adrenalin chloride, rather than the adrenalin base, is the usual starting point in prescription compounding. Some discussion is necessary, therefore, of the composition and properties of this preparation and of the precautions necessary to its conservation.

Commercial solution of adrenalin chloride contains one part per thousand of adrenalin chloride dissolved in physiologic salt solution with about one-half percent of chloretone. It is faintly acid in reaction, tastes of chloretone and salt, smells of chloretone, and, when fresh, is nearly colorless. Stored away from strong light and heat, with the seal unbroken, the solution will retain its activity for a long period. When, however, the stopper is removed and contact with air permitted, a new factor is to be considered. The oxygen of the air is destructive of adrenalin. Given good storage, the precaution most essential to the preservation of the commercial solution of adrenalin chloride, is to minimize contact with air. Only so much as is required for immediate use should be removed from the stock-bottle, which should be stoppered promptly and tightly. With ordinary care in handling, there is, within reasonable time, no necessity for serious loss through deterioration.

The oxidation that occurs upon undue exposure to air, is evidenced by change of color. The solution becomes pink, then red, then brown and a brown precipitate settles out. This fact is not without practical application since the color constitutes a rough, but fairly reliable index, of the potency of the solution. Experiments have been made to discover, if possible, some relation between the shade of color and the amount of deterioration. Solutions have been exposed freely to the air, the several changes of color observed, and physiological assays made from time to time. Of course, any quantitative statement based on personal estimate of a shade of color, is of necessity very crudely approximate. Bearing this in mind, however, and limiting the statement strictly to the undiluted commercial solution, we may say that so long as the color is not deeper in shade than what most persons would call pink, the loss of activity is practically negligible. When it becomes red, the loss of activity is quite measurable. It may amount to 10 or 20 percent of the whole. When brown, with the brown precipitate, the solution should be rejected, though even such solutions often retain considerable activity.

Aside from the physiological assay, which is too complicated for use in the pharmacy, I know of no entirely reliable assay method for adrenalin. Several colorimetric methods have been proposed, but there is none that I dare recommend as wholly accurate and trustworthy. The colors are often fleeting and vary in tint with the nature of the sample. Certain of the proposed reactions, also, are by no means specific for undecomposed adrenalin.

A rough qualitative test, to show the presence of active adrenalin in the commercial solution of adrenalin chloride of the composition already stated, is based on

its conduct with ferric chloride. As you are aware, ferric chloride gives striking and more or less characteristic color reactions with many of the phenols. Catechol, the parent phenol of adrenalin, gives, in dilute aqueous solution with a very little dilute ferric chloride solution, a brilliant green color, which, upon careful addition of very dilute alkali, passes through a series of color-changes from bluish-green to purple-red. Under like conditions, adrenalin acts similarly. The catechol nucleus is responsible for this reaction, so that it is not peculiar to adrenalin. If, however, dilute solutions of catechol and adrenalin chloride be treated with a little very dilute ferric chloride solution without subsequent addition of alkali, and if the two solutions be allowed to stand in the air for some minutes, a difference in their behavior will manifest itself. In the case of catechol, the green color persists; in that of adrenalin, it changes slowly to pink or red. While the test is not absolutely final, it is fair to conclude that a commercial solution of adrenalin chloride retains some activity when a sample, highly diluted, gives with a drop of very dilute ferric chloride solution a green color changing soon to pink or red. Many foreign substances interfere with the test, so that it may not be applicable to adrenalin in mixtures.

Having at hand a solution of adrenalin chloride known to be active, it remains to consider the precautions to be observed in dispensing it, alone and in mixture. Certain mixtures are chemically rational and therapeutically useful. If one is proposed, however, of whose feasibility there is doubt, let me counsel conservatism. Where possible, mixtures are best avoided; adrenalin is a sensitive substance, easily changed by many chemical reagents.

Chiefly to be feared, are alkalies and oxidizing agents. Almost any substance that, chemically, would be classed as an oxidizing agent, is more or less injurious to adrenalin. In this category are such substances as oxygen itself, free chlorine, bromine, iodine and their oxy-acids, permanganates, chromates, nitrites, salts of easily reducible metals, etc. Iron is extremely troublesome, because of its wide distribution and because a very minute amount will suffice to shorten measurably the life of an adrenalin solution. Traces of iron in other chemicals, in distilled water and even in glassware, are decidedly to be reckoned with. Of course, iron utensils should never be brought in contact with adrenalin.

Alkalies are no doubt destructive directly, but mainly they are pernicious, because they very greatly accelerate the destructive action of oxidizing agents. A faintly alkaline solution of adrenalin exposed to the air, will lose its activity very quickly. Such solutions are often prescribed, but ought not to be dispensed, unless confirmed by the physician after he has been informed of their instability. Every solution of adrenalin that is expected to retain its activity, should show a faint acid reaction. I am acquainted with no satisfactory expedient for preparing a stable adrenalin solution, that is not slightly acid. Organic acids and weak mineral acids are not very effective, unless present in considerable amount. A minute trace of a strong mineral acid, that is to say, a highly dissociated acid, is to be preferred.

In conformity with the last statement, the non-oxidizing acids, in reasonable dilution, are not injurious to adrenalin. Dilute sulphuric, sulphurous, hydrochloric, phosphoric, boric, salicylic, acetic, tartaric, citric,—in fact, most of the

acids commonly used in medicine,—are harmless. Oxidizing acids are of course objectionable.

Salts of the common alkaloids, of the alkali metals and, broadly, of the light metals generally, are not intrinsically harmful. If, however, their acid radicals are of weak,—that is to say, slightly dissociated,—acids, they may indirectly diminish the resistance of the adrenalin to oxidation by partial replacement of the trace of free strong acid normally present.

Phenols of the types of carbolic and cresylic acids are harmless. Ordinary camphors, terpenes, and similar bodies are not injurious, save in so far as they may be to a certain extent carriers of oxygen. Most aldehydes of high molecular weight, alcohols and ketones, are probably harmless. Formaldehyde, however, is directly destructive to adrenalin, and the two are wholly incompatible. As little as 1/10 of 1% of formaldehyde added to solution of adrenalin chloride will render it quite inert within a few hours.

In the foregoing statements of incompatibility, exhaustive accuracy is not pretended and doubtless there may be found exceptions. The purpose is merely to characterize certain broad types. An elaborate table of specific incompatibles, even were the data available, is beyond the scope of this paper.

To exemplify the use of these statements, and to emphasize some of the most important points, it will be well to examine and comment upon a few prescriptions. Some of these were submitted for criticism in the regular course of business; some are written arbitrarily to illustrate a particular case. All, however, are such as might be met with in the experience of any pharmacist.

1. ℞ Solution Adrenalin Chloride..... 1 fluidrachm

Let us begin at the beginning. This prescription requires only, that a fluidrachm be dispensed from stock, yet I venture to say that if filled carelessly, the solution will, in many instances, undergo deterioration far more rapidly than the same solution in the stock-bottle. Certain precautions are recommended that will apply not only to the present case, but to all prescriptions containing adrenalin. Either a glass-stoppered bottle should be used, or else the lower end of the cork should be covered with waxed tissue. The vial should be scrupulously clean and in particular it should be, as nearly as possible, free from alkali and iron in soluble form. It is advisable, therefore, to wash out all bottles with strong hydrochloric acid followed by much distilled water. This, however, is only a temporary expedient, and the best plan is to select an insoluble glass.

2. ℞ Sol. of Adrenalin. Chloride..... 1 volume
Distilled water or physiologic salt solution..... 9 volumes

All the comments on the last prescription, apply equally to this. In addition, one should make sure that the distilled water or physiologic salt solution, is free from alkali and iron. It is a good plan, also, to use water or salt solution that has been freshly boiled and cooled. It has already been remarked that the commercial solution of adrenalin chloride is faintly acid,—a condition necessary to its stability. Here, this acidity is reduced, by dilution, to 1/10 its original proportion. In many ordinary bottles, there is sufficient soluble alkali to neutralize completely this trace of acid, and so to determine the rapid oxidation of the adrenalin. The life of this solution, therefore, would be greatly prolonged by the addition of chemically pure hydrochloric acid, in such proportion that the finished solution

contains about 1/100 of one percent of the absolute acid. Care should be taken that the acid itself is as nearly as possible free from iron, very appreciable amounts of which are present in many lots of, so-called, chemically pure hydrochloric acid.

Even when quite sterile at the outset, solutions like the one under consideration are liable to contamination in use. To prevent the development of fungus, a mild antiseptic may be added. Saturation with chloroform or chloretone would improve such solutions.

3. ℞ Adrenalin ..... ¼ grain
Cocaine ..... 5 grains
Sodium chloride, C. P..... 4 "
Boric Acid..... 10 "
Chloretone ..... 2½ "
Distilled water, sufficient to make..... 1 fluidounce

This solution would probably deteriorate fairly rapidly. There should be present some mineral acid stronger than boric. Very suitable would be hydrochloric acid, C. P. in quantity sufficient to saturate the adrenalin and cocaine, and leave an excess of about 1/100 of one percent of absolute acid in the finished solution. Also the boric acid should be free from iron,—an impurity very common in even the medicinally pure acid.

4. ℞ Sodium bicarbonate
Sodium borate
Sodium chloride, aa.....2.5 grains
Thymol .....1/80 grain
Sol. Adrenalin Chloride..... 1 fluidrachm
Distilled water, sufficient to make..... 1 fluidounce

Nose and throat specialists sometimes order spray-solutions similar to this. Usually they are designed to be slightly alkaline, so that the addition of acid, even if otherwise advisable, would defeat the intention of the prescriber. In the present case, it would be almost useless to add hydrochloric acid, unless in quantity equivalent to the whole of the sodium bicarbonate and sodium borate. This is of course inadmissible. The remedy is, with the consent of the prescriber, to put up the adrenalin solution separately, instructing the patient to add, in proper proportion, to each dose of the spray-solution immediately before use. If dispensed as it stands, it will become inactive in a very short time.

5. ℞ Zinc sulphate..... 0.05 gramme
Cocaine hydrochloride..... 0.2 "
Adrenalin solution..... 10 drops
Fennel water, B. P., sufficient to make..... 15. grammes

This prescription, dispensed by an English pharmacist on the order of an oculist, underwent marked deterioration within a few days. In reply to inquiry as to the cause, certain possibilities were pointed out. First, it is to be noted that the ten drops of adrenalin solution were diluted to about 15 cc., thus reducing the acidity of the adrenalin solution to such an extent that the trace of alkali yielded by most common glass bottles would be fatal. Further, zinc sulphate very often contains iron. This salt and, indeed, each of the ingredients, as well as the bottle itself, should be tested for iron. It is highly probable that one or both of these causes was accountable for the deterioration. The remedy would be to use materials and container as nearly as possible free from iron and alkali, and to add, as

already recommended, hydrochloric acid, C. P., up to 1/100 of 1 percent of the finished solution.

6.	℞	Mercuric chloride	¼ grain
		Sol. Adrenalin Chloride	2 fluidrachms
		Water, sufficient to make	1 fluidounce

When this prescription was compounded by a pharmacist, there appeared,almost immediately, a slight grey precipitate, the solution becoming red. The precipitation was due, of course, to the reduction of the mercury, and the color, to the oxidation of the adrenalin. That the reaction occurred immediately, resulted, perhaps, from the use of slightly alkaline tap-water. Adrenalin chloride and mercuric chloride solution may be mixed, without immediate destructive reaction, if there is present a little free hydrochloric acid. Even with this precaution, however, the adrenalin is destroyed within a comparatively short time. This prescription should not be dispensed.

7.	℞	Cocaine hydrochloride	9 grains
		Sol. Adrenalin	1½ fluidrachms
		Iodine	4 grains
		Cherry laurel water, B. P.	2 drachms
		Glycerin, q. s., to make	1 fluidounce

This prescription is copied from the Pharmaceutical Journal, Vol. 16, page 484, where it is condemned, because of the evident incompatibility between iodine and cocaine hydrochloride. It is further asserted, however, that the formula might be serviceable if the cocaine hydrochloride were omitted,—an obvious error since iodine is quickly destructive to adrenalin.

8.	℞	Adrenalin chloride	6 grains
		Camphor	1 ounce
		Phenol	½ ounce
		Olive Oil	8 ounces

This formula is not practicable by reason of the comparative insolubility of adrenalin chloride in the mixture. A physician stated that a very similar prescription was being filled for him regularly. If so, it is probable that an examination of the product he was using would discover either the almost complete absence of adrenalin or the presence of ingredients not mentioned in the formula.

9.	℞	Solution Adrenalin chloride	1 fluidrachm
		Sodium benzoate	1 grain

The trace of free hydrochloric acid of the adrenalin solution will be largely replaced by the less efficient benzoic acid. The solution will keep fairly well but will be less resistant to oxidation than the un-modified solution of adrenalin chloride.

To summarize in part,—the following considerations are of first importance in dispensing:

Deterioration of adrenalin solutions is usually due to oxidation, either by the oxygen of the air or by an added oxydizing agent.

Oxidation is retarded by acids, but accelerated by alkalies. Solutions alkaline in reaction, ought not to be dispensed.

In retarding oxidation, a trace of strong acid is, in general, more efficient than the equivalent amount of a weak acid. Solutions acidified with a trace of a weak acid, may be dispensed, but will not be very stable. Resistance to oxidation, other things being equal, seems to be a function of the number of hydrogen ions in a

unit volume of the solution. The acid should be used, therefore, not in proportion to the amount of adrenalin chloride present, but in proportion to the total volume of the finished solution. One one-hundredth of one percent of absolute hydrochloric acid, is a suitable proportion.

Prescriptions including oxidizing agents, should not be dispensed. Iron salts, in particular, are to be avoided. Containers, distilled water, and all materials entering into the prescription, should be as nearly as possible free from iron.

Glassware containing much soluble alkali should not be used.

Contact with air should be minimized.

WHAT PERCENT OF THE PRESCRIPTIONS DISPENSED IN YOUR STORE CAN YOU CONSCIENTIOUSLY DECLARE TO BE DISPENSED WITH FRESH DRUGS AND CHEMICALS?

CORNELIUS OSSEWARD.

The frequency with which we see druggists and very often pharmacists also, lay particular stress, in their advertisements, that nothing but absolutely fresh drugs and chemicals are used in dispensing, is my excuse in asking the above question.

Whenever I see such an advertisement or announcement, it reminds me of another too frequently in print, n. l.

"PRESCRIPTIONS OUR SPECIALTY."

Our intentions may be good; we may think that we are dispensing fresh drugs; we may tell the dear public that we are specialists in dispensing, but will it stand investigation?

I am convinced that, under the present conditions, it is often impossible for the pharmacist to make such a statement and speak honestly, and that the firm using the largest sign "PRESCRIPTION SPECIALIST," or "PRESCRIPTIONS OUR SPECIALTY," do not possess a Pharmacopœia or National Formulary, and that the common utensils required in dispensing are conspicuous by their absence.

As there has been a great deal of that kind of advertising, which, after a little investigation could not stand the test, it is certainly refreshing to note the tendency for more honest and true statements.

Should we as pharmacists not be very careful how we advertise, how we write our copy? *Be sure* that you can *deliver* that which you promise.

In order to prove to you that we as pharmacists cannot at all times supply fresh drugs because we do not know about them, let me ask you,—

Are you giving your prescription stock as much attention as it requires?

Are you buying the right kind of stock in the right quantity? And are you taking proper care of this stock while in your possession?

Again, how long have these drugs and chemicals been on the jobbers' shelves? And how much care has the jobber given to the proper storing of his goods?

Is it not true that the average pharmacist, with the exception of the larger stores, buys mostly through the jobber, and it is therefore proper to ask whether the jobber looks after his stock, and stores it properly?