LIQUOR OPII COMPOSITUS,

OR

COMPOUND SOLUTION OF OPIUM.

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LIQUOR OPII COMPOSITUS. (COMPOUND SOLUTION OF OPIUM.)

By Edward R. Squibb, M.D.

In the early part of 1859 the writer of this note completed a design previously formed and less definitely executed, of offering for general medical use a liquid preparation containing only the useful anodyne and hypnotic constituents of opium, and of uniform strength.

The design originated in a desire to improve upon the advantages of the "opium titré" or assayed opium of French pharmacy, and to imitate, with improvement, if might be, some of the advantages claimed for the nostrums known as Battley's "liquor opii sedativus," and McMunn's "elixir of opium."

Such a preparation was made, and, under the name of liquor opii compositus, was placed in the hands of several physicians who were supposed to be intelligent close observers, and who had been long familiar with the various preparations of opium and their effects in use. These trials, though not very numerous, resulted in the main so favorably that, after continuing them through the year 1859, a paper was prepared upon "opium as a therapeutic agent," containing a minutely detailed practical working formula for the preparation of liquor opii compositus, and strongly recommending it for trial in general use, and for introduction into the then approaching revision of the U. S. Pharmacopœia, if it should sustain its promised useful character. This paper was published in this Journal for March, 1860, and may be found in Vol. VIII of the third series (Vol. 32, whole number), at pages 115 and 120 et seq. The preparation was not advertised nor pushed in any way, either publicly or privately, but was simply announced for sale on the writer's price lists, with a recommendation for trial, and was allowed to make its own reputation, and seek its own level of value. In 1862 it had been much more extensively tried, but was refused admission to the Pharmacopœia by the Committee of Revision,—the Committee adopting instead of it the present formula for tinctura opii deodorata. With this latter preparation it was at once put in fair open competition, the two preparations being offered side

by side, with a fair statement that one had been rejected and the other adopted by officinal authority, and with the no inconsiderable inducement of 20 per cent. difference in price in favor of the officinal preparation. Beside, the officinal tinctura opii deodorata was always made from assayed opium, and was uniform in strength with the liquor opii compositus, with which it was placed in competition. The Pharmacopœia does not require the tinctura opii deodorata to be made by assay, but this was done to secure the competition against any disadvantage through want of uniformity in strength. The liquor opii compositus is always made of the strength indicated in the officinal tinctura opii, or laudanum, if the laudanum be made of good powdered opium as it should be. Such laudanum always contains at least four grains of morphia, which is equivalent to about five grains of crystallized sulphate of morphia in each fluidounce. Since 1867 they have been placed side by side upon all the price lists issued by the writer, and until recently with notes fairly setting forth the characteristic points of each. Diligent inquiries have been made in regard to the comparative value of the preparations, and whenever these inquiries have been answered the preference has been given to the compound solution. The sale of both has increased steadily year after year, but the sale of the compound solution has increased much more rapidly than that of the deodorized tincture, and is now more than ten times greater. The regular and steady increase in the demand for the compound solution during the past eleven years having now increased its production in the writer's hands to over eight hundred pounds a year; and the probability that many pharmacists make it for themselves, induces him to undertake a revision of the formula, in order to remove some objections to the present formula, which appear to have been established on good grounds.

The first and principal objection to the present formula is that the odor and taste of ether is disagreeable to most persons, and to many nauseating and hurtful. The increasing use of ether as an anæsthetic, and the nausea, vomiting, and natural disgust produced by it when so used, and the frequent necessity for an anodyne after anæsthesia, renders it of some importance that the anodyne should not contain the agent which has excited the

nausea and disgust, but should rather contain some corrective or corrigent to this tendency to nausea. The compound spirit of ether was used in the preparation chiefly as a preservative agent, to prevent change in the solution, but also to have whatever effect it might, in so small a proportion (3 minims in 24), in favorably modifying the action of the opiate. Dr. Physick and many other excellent authorities had the habit of associating the true Hoffman's anodyne (made with heavy oil of wine) with their opiates, and the habit was confirmed by their observation of the effects obtained. It, however, could not be introduced into the compound solution of opium in sufficient quantity to be very effective, even as an adjuvant, and it is therefore highly probable that its chief agency has been that of a preservative against change in the preparation, and therefore that it might be replaced by some other preserving agent, even if objectionable only in a small proportion of the cases in which it is used, without altering the intrinsic character or value of the preparation.

The second objection to the compound solution of opium was that when long kept in a bottle only partially full, particularly when thus kept in warm climates, or in a warm place in a dispenser's store, it would gradually lose the odor of ether, and assume that of acetic ether. This change was rarely completed in less than two or three years, but numerous instances have been met with where every trace of both ether and heavy oil of wine odor had disappeared. Such specimens, when carefully tried, were found to possess their full original anodyne and hypnotic value, and gave to some good observers the impression or conviction that the acetic ether thus spontaneously generated was an improvement upon that which it replaced. Through watching this suggestion during the past two years, and reading somewhat upon the uses of acetic ether in continental Europe, where it is occasionally prescribed, the conclusion has been reached that even in small quantities it has a pleasant stimulant effect, and that its odor and taste are refreshing and agreeable to a large majority of people, or indeed to almost all. And finally, that if medicinal at all, it is so to nervous susceptible persons, and always in the direction of favorably modifying the well known disagreeable effects of opiates.

These are the two objections that are to be met, and, if possible, removed, in the revision of the formula for compound solution of opium. The much more forcible objection of a complicated formula, and a multiplicity of detail involving sufficient knowledge and skill to make a correct opium assay, can only be met by the arbitrary opinion or judgment, that he who cannot make such a preparation when all the details are laid down step by step before him, is unfit to be trusted with the dispensing of medicines. It has been made, and skilfully made, by persons of only ordinary pharmaceutical acquirements; and many have refused to make it from the insufficient reason that it involved too much pains and labor. As the essential points or supposed advantages of the preparation,—namely, its uniformity of strength independent of the character or quality of the opium from which it is made, and its freedom from many, if not all of the useless and hurtful constituents of crude opium, whilst retaining the useful constituents in their natural combinations,—as these points are considered essential, are the only objects of the process, and can be attained in no better or more simple way known to the writer, this objection must stand with its full and acknowledged weight against the preparation, with the simple remark that in pharmacy, as in other arts, the best results are not often attainable without commensurate skill and labor.

So much for the revision of the formula, in regard to the objections that have been justly raised against it. The next question that arises is, can it be therapeutically improved? And to this, within the knowledge and judgment of the writer, and of those observant physicians with whom he is in frequent intercourse for counsel and advice, it must be answered that it probably cannot be materially improved in this respect. All opiates, no matter how made or how used, will disagree with many persons, and with some more than others; whilst that opiate which is best borne by some sensitive persons may be badly borne by others. All opiates will constipate almost all persons under all ordinary circumstances, and will produce a nervous reaction proportionate to the initial action, or at least in proportion to the initial over-action or overdosing. Then as all derivatives of opium must in the nature of things partake of the character of opium somewhat

in the relation of cause and effect, it seems most rational to accept together some of those advantages and disadvantages which long observation has shown to be as inseparable as cause and effect, and to seek, rather, by combination with other known agents, or by the subsequent use of corrigents, to remedy the disadvantages in those cases where these are of sufficient importance to demand medication. It is nevertheless now pretty well established, not only that some opiates disagree less than others with sensitive persons, but that some opiates are more generally acceptable and beneficial, and less disturbing than others, and this for reasons of two kinds: First, by excluding some of the disturbing agencies of the opium, and second, by more or less skilful combinations with corrigents. All that can be safely said of the past career of this liquor opii compositus is that it disagrees with a smaller number of sensitive persons, both in its primary and secondary effects, than most other preparations of opium, and that it is more pleasant in its effects than other preparations of opium, or the salts of morphia, in a very considerable proportion of cases, if not generally.

In the deliberate thought and attention given to this preparation during the past few years in connection with its increasing usefulness, it has sometimes seemed doubtful whether the simple depurated watery solution of opium adjusted by assay, and mixed with one-fifth or one-sixth of its weight of alcohol to preserve it from change, would not be the best practical form in which to offer it for therapeutic application. Such a preparation would be called simply liquor opii, and may be made by the formula to be given. This would leave all attempts to modify, correct, or remedy the unpleasant effects of the opiate to the extemporary judgment of the physician, where perhaps they more appropriately belong, because they would be better adapted to individual cases, and would yield a preparation that might be used by hypodermic injection.

This course would be now adopted in the revision of the formula, were it not that the disagreeable taste and smell, and the nauseating effects of opiates, are so objectionable to a large proportion of patients, and that physicians in general are not skilful in the use of corrigents, and therefore not unfrequently fall, or

are led into practices which, to say the least, do not always tend to improve the therapeutic action of their remedies,—the use of sugar-coated pills, for example. It is therefore mainly to cover the taste and odor of the opiate, to render it more acceptable in delicate conditions of the stomach, and to give it a direction or tendency opposite to that of nausea, that a small proportion of acetic ether and purified chloroform are now introduced into it instead of the compound spirit of ether. If these new ingredients have any important medicinal effect, it will surely be in a direction opposite to the natural nauseating and depressing effects of the opiate, and therefore they are safe, with a reasonable chance of being useful.

Such good effects may well be expected from chloroform, and might be secured if the chloroform could be well introduced in larger proportion, for the following principal reasons, which have led the writer to use it in the formula. Soon after the internal use of chloroform was practised it was found to be sedative and hypnotic, or to have very much the same therapeutic effects now attributed to chloral, and was by some physicians associated with opiates, and particularly with the salts of morphia, with very good results in favorably modifying the action, and controlling the after effects, as nausea, anorexia, headache, depression, etc. It was, however, practically very difficult to get the two substances in solution together within the limits of an ordinary dose without inconvenience from the pungency of the chloroform, and the best results were obtained from the clumsy and inconvenient plan of mixing them with thick syrup or honey. The burning effect of the chloroform upon the mouth, fauces and stomach, though of short duration, was objectionable, and thus the association of the two substances, though proved to be eminently advantageous, never came into general use. It was, however, sufficiently used and appreciated to attract the attention of quackery, and the nostrum called "chlorodyne" was the result. It is often wonderful to see how squeamish and critical physicians and patients are to the disadvantages and inconveniences of legitimate extemporaneous mixtures, which, when served to them in the plausible tone of quackery, lose all their disadvantages, and come out afresh with sensational novelty. Chloroform

associated with morphia salts forms the therapeutic basis of the nostrum "chlorodyne," and the extraordinarily incongruous and irrational mixture of molasses, peppermint, capsicum, cannabis, hydrocyanic acid, perchloric acid, and all the others, if there be more, forms a mere vehicle and blind for the attempted secretion of this old and valuable combination. When, however, it came out in this new dress, at the call of the tin trumpet of quackery, many physicians in the very cities where the extemporaneous use of the combination originated became loud in its praise, and their patients found no difficuly in swallowing it at double price. Through the now waning use of this "chlorodyne" and its numerous imitations, many physicians, and some of them without being yet aware of it, have been again taught, on a larger scale, that there is a value in the association of chloroform with their opiates for internal use. But to realize the best effects of this combination the chloroform must be in the proportion of about one fluidrachm to the grain of morphia salt, or about eight or ten minims to the ordinary dose. This makes a mixture which, though not too pungent for many uses, is so rarely needed as to be objectionable for common use.

These considerations led the writer to adopt purified chloroform as an ingredient in the new formula for liquor opii compositus, and a series of experiments was undertaken to determine how much chloroform could be introduced, and still have the solubility or miscibility of the preparation in water secured. This proportion was found to be unexpectedly small, even when the solution was made to consist of one-half its volume of alcohol, thereby taking the character of a tincture rather than a solution. One minim in twenty-five, or one-twenty-fifth of its volume, was found to be the maximum quantity of chloroform which would be permanently held in solution when the twenty-five minims of the preparation was dissolved in one fluidrachm of water or more. This solution when made with a fluidrachm of water was considered a little too near to the boundary line of precipitation of the chloroform, and a little too pungent or biting for common use, and therefore the proportion of chloroform was reduced to one minim in thirty minims of the finished preparation, and the whole formula as finally determined upon was as follows:

Depurated, assayed solution of opium, (Equal to one-third of a grain of sulphate of morphia.)	14 minims,
Stronger alcohol,	13 minims.
Purified chloroform,	1 minim.
Acetic ether, s. g. 0·880,	2 minims.
Maximum dose,	30 minims.

In the very full dose of 25 minims there will be,—

Of the opium solution (equal to about one-quarter of a grain of sulphate of morphia),	11·67 minims,
Stronger alcohol,	10·83 "
Purified chloroform,	·83 "
Acetic ether,	1·67 "
	25·00 "

In the average adult dose of 20 minims there will be,—

Of opium solution (equal to about one-fifth of a grain of sulphate of morphia),	9·33 minims,
Stronger alcohol,	8·67 "
Purified chloroform,	·67 "
Acetic ether,	1·33 "
	20·00 "

This preparation, when dropped from a common one-ounce vial, gives about eight hundred and twelve drops to the fluidounce;* or about one and seven-tenths (1·7 drops) drops to the minim. Therefore thirty-four drops is about equal to twenty minims. Thirty drops is perhaps the more common usage as the ordinary adult dose, while twenty-five drops is often sufficient for adult females, or even adult males who are susceptible to opiates.

It is occasionally required in double, or even in three times the maximum dose as above given, and then will of course con-

* The first two fluidrachms dropped from full bottle, 190 drops.

The second two "	176 "
The third two "	201 "
The fourth two "	246 "

tain twice or three times the quantities, equal to two-thirds or one and one-third grains of sulphate of morphia. These doses are, however, under ordinary circumstances poisonous; and it is always best with this, as with all other opiates, to give them in judiciously timed divided doses until the object or indication is *nearly* accomplished, and then stop.

When opiates are given incautiously in large doses, they often seem to meet the indications to their use with a shock or concussion, overwhelming all the powers; and in proportion as this impression is profound and continued, and in proportion as it over-reaches the desired object, in the same proportion is the subsequent reaction, producing depression, anorexia, nausea, headache, constipation, etc. Now in medicine, as in mechanics, it would be irrational to expect to control a reaction independent of control of the initial action, and therefore opiates are not justly chargeable with the results of this not uncommon misuse. On the other hand, however, it is necessary to avoid the very small doses which serve only to stimulate and excite the sensorium; and therefore no direction for dosing can be given that will be more than usefully suggestive to common sense and good judgment, acting upon a clear conception of just what is required to be done, and how easy it is to overdo this.

The plea for assayed preparations in medicine and pharmacy, in order to attain some degree of accuracy and uniformity in therapeutic practice and results, is well illustrated in the instance of opium. It is well understood that hardly any two lumps in a case of ordinary opium yield the same proportion of the useful alkaloids, and that the different lumps have as great a variation as from five per cent. in some, to ten or eleven per cent. in others. It is also well known that by the escape of moisture the proportion of alkaloids is constantly varying until the opium is quite dry. It is also well known that opium is *not* the concrete juice obtained by incision from the unripe heads of Papaver somniferum, but is a varying proportion of this juice mixed with a heterogenous mass of foreign matter in a more or less solid condition, and that the productive or unproductive seasons, and the variations and speculations in price, have an influence in the yield of the alkaloids and also in the amount of foreign matters

admixed. If there be any who believe that the opium of the markets is wholly, or even in greater part, constituted of the juice of the capsule obtained by incision as described by the books, it is only necessary for them to divide the whole number of the population of the part of Asia Minor which produces opium, into the number of pounds which constitutes a crop, to prove that it is impossible for any such number of people to collect any such quantities in any such way. It is also known that there are different grades of quality in opium, which *may* be judged by the appearance; and different grades of quality which *cannot* be judged by the appearance, no matter how expert the judge may be. Crude opium, to be officinal, must contain "at least 7 per cent. of morphia." Then this crude opium in drying loses an average of 20 per cent. of moisture. Therefore dried or powdered opium made from crude opium which is just within the officinal minimum limit and no better, will contain 8·75 per cent. of morphia.

The writer has recently seen a small lot of opium that, when dried, yielded a powder containing nearly 15 per cent. of morphia, and knows from actual observation that by appearance, on very critical inspection, it could not be distinguished from another lot which, under the same management, yielded only 12 per cent.; and yet there was only a difference of about $1.50 or less per pound in the price.

Beside this, opium being a mixture made up for price and profit at the place of production, and being of limited production, but of almost unlimited demand, has of late years assumed the character of a manufacture rather than a natural product; and its practical standing in the markets to-day in regard to its dilutions and adulterations at the place of original production is not very different from that of woolen goods in regard to shoddy. Hence the better grades of opium, like the better grades of woolens, are produced in comparatively small quantities for the comparatively small demand at higher prices, and these grades, naturally enough, fall into the hands of the makers of morphia salts, where intrinsic value is closely studied in the interests of pecuniary gain.

Again, so localized and so limited is the production of the

valuable varieties of opium, and so wide-spread and insatiable the demand for opium,—four-fifths of it, at least, being probably consumed as an intoxicant,—that a "ring" of speculators could, and did form a "pool" last year, and so controlled the product and the markets as to run the price up to more than double, and during one period to about three times the ordinary cost, and to maintain such prices for nearly the entire crop, with such signal pecuniary success as to warrant the prediction of future similar speculations. Indeed, at this moment opium is again on the rise, with the possibility, if not the probability, that it is again "cornered" by a "ring." All this will probably have the very natural effect of stimulating the production; but the production will be stimulated in two ways: not only to cultivate more poppies and make more juice, but also to make more opium from the juice,—that is, debase it still farther in the manufacture, just as wool is made to go farther when the supply is short of the demand, and the price consequently high.

Now if these statements and deductions be true, and have any value in or any bearing upon medicine and pharmacy, they indicate one thing, and teach one lesson which is optional with us to learn or not, and that is, that the comparatively small portion of opium which is used in legitimate medicine and pharmacy should be used only by assay; and that such opium and its preparations should be, by assay, brought to a definite uniform medicinal strength. But from the variation in the various lumps of opium of the same case it is manifestly impossible, or at least impracticable, to assay it with useful accuracy in the crude moist condition. It must be either dried and powdered, and the powder be assayed, or it must be extracted, and the extract be assayed. Opium, then, is an exception to the rule which teaches all careful physicians and pharmacists never to buy drugs in powder. And yet, unless assayed, it is the most unsafe of all drugs to buy in powder. No plan is so good or so safe as to dry and powder the opium, and then assay the powder by extracting that; because, if carefully dried and powdered without too much heat, the quantity and quality of the useful alkaloids are not materially altered, whilst a large proportion of the useless and embarrassing extractive matter is rendered insoluble in the dry-

ing and powdering process. Beside, it is only by drying and powdering that a homegeneous product is obtained, every part of each package of which represents the whole. If a physician or pharmacist buys a pound of powdered opium, the assaying of 150 grains or so of this will indicate the quality of the whole. But if he buys a lump of crude opium and assays any part, or even two or three parts of it, the assay may not, and in all probability will not, represent the whole. He may make the whole lump into a strong tincture or solution by extracting it, and assay a portion of this solution or tincture, with the same ultimate result, but the assay is then less simple and more difficult.

This then is the chief, though not the only merit claimed for this liquor opii compositus, that it is made by assay, and therefore of practically uniform strength, entirely independent of the quality of the opium from which it is made.

This process of assay is not a highly critical scientific process which gives account of every tenth, or even every quarter of a per cent. of the useful alkaloids contained in the opium, but the aim is simply to come within one per cent., or thereabout, of the medicinal value and efficacy of different parcels of opium in its power to produce sedation, and to relieve pain in disease. Whilst a critical morphiometrical assay, or an analysis of opium, is one of the most difficult processes within the writer's knowledge, and probably has never been once attained in his thirty years' experience, a practically useful and sufficient process, by various methods, is so simple and easy as to be within the capacity of any person who is at all fit to be trusted with the handling of potent agents in their application to medicine. The first steps of that simple process of assay which is preferred by the writer are those by which the solution of opium which characterizes this liquor opii compositus is depurated, or freed from extraneous matters, whether these be hurtful or simply useless. And this is the second and only other important merit claimed for the preparation. By rejecting much of the resinous, gummy, nauseous, and otherwise hurtful constituents of the heterogeneous mixture called opium, a real practical advantage is obtained; whilst the retaining the useful alkaloids in their *natural combi-*

nations, associated with only that part of the coloring matter and extractive which, like the useful alkaloids, are soluble in both water and alcohol, and insoluble in ether, must be considered as important advantages. Hitherto the preparation has been an aqueous one, or at least contained only one-eighth of its volume of the mixture of alcohol, ether, and heavy oil of wine. But it is now so doubtful whether there is any real advantage in this, that the point is abandoned in order to secure the permanent solution of the chloroform by largely increasing the proportion of alcohol. Hereafter the preparation will contain about half its volume of stronger alcohol,—that is, will be of about the same alcoholic strength as the officinal tincture of opium. This materially disturbs and diminishes the appropriateness of the name, since "liquor" is commonly accepted to mean an aqueous solution, whilst "tincture" is as commonly accepted to mean an alcoholic solution. All good authorities, however, apply the word "tincture" in a technical sense to solutions where the solvent is only half alcohol, or even less. The name, however, cannot now be wisely changed, and the only circumstance which supports its equivocal appropriateness is that the large proportion of alcohol is not present as a solvent of the opium products, nor as a vehicle, since the water performs both these parts, but merely as a preservative agent, and as a solvent and protector for the chloroform and acetic ether; and it therefore may be construed to enter into the nomenclature with its more intimate associates under the word "compositus," as one of the compounding ingredients.

The preparation may perhaps not unfairly be criticised as unstable, from the great volatility of both the acetic ether and chloroform, since these will have a tendency constantly to escape from it during use. But when it is remembered that these are not essential to its primary medicinal efficacy, and that if entirely evaporated out the medicine would be but one-tenth stronger, the criticism will not have much force. A much more forcible objection to the preparation is often made in regard to its costliness. This objection cannot be satisfactorily met, and need not be attempted, since those who do not recognize the necessity or the value of the time, labor and skill involved in it, and are not

willing to pay a liberal profit upon these as invested in it, of course should not make or use it,—and will not, no matter what might be said in attempted justification of the cost. Upon an average it will represent about one-tenth of its weight of powdered opium; and it will not remunerate the maker unless it yields him about two and a half or three times the cost of that proportion of the best powdered opium.

It happens that the useful constituents of opium are all soluble in both water and alcohol, and are insoluble in ether; whilst a very large portion of the useless and hurtful constituents are insoluble either in water or in alcohol, or when soluble in both are also soluble in ether. Taking advantage of these circumstances the opium is subjected to the action of these solvents in succession, the successive residues being rejected, and the resulting extract is diluted to form the depurated solution. A small portion of this is assayed, and the result of the assay is applied, by multiplication to the whole, and this is then diluted to a definite degree by the addition of the other ingredients and water. Merely to state this general plan or outline of the process without the detail necessary to put it in practice would be of no use, and would really defeat the object of this paper, since that object is not more to convince the reader of the necessity for such a preparation, than to teach him a good practical way of making it for himself, and perhaps, also, to offer what may be a useful lesson in practical pharmacy. Beside, where broad and apparently exaggerated statements are made in any particular interest there is always room for suspicion of advertising; and the cause for suspicion is strengthened when any reserve can be detected, or when any link or point is missing in what should be clear inductive detail. It oftens happens to the writer, in reading what at first sight appears to be a plain open and sufficient detail of a process, to have his suspicion aroused by a missing link or an ambiguous sentence, and therefore the casual reader must excuse any prolixity in detail that may appear unnecessary in giving the following formula and process, since this prolixity, at least, is not caused by having something to conceal.

In giving the formula and process in the U. S. P. officinal weights and measures, nearly or practically accurate equivalents

of the metrical or decimal system of weights and measures are also given because they will be found very convenient to some operators, and because it will serve to familiarize those who read them with the values in this system which is coming into use.

Take of powdered opium, 1543 grains or 100 grammes.
Stronger ether,
Purified chloroform,
Acetic ether,
Stronger alcohol,
Water, of each a sufficient quantity.

Put the powdered opium in a suitable vessel of not less than 25 f℥. or 750 cc. (cc. cubic centimetre,—30 cc. to the f℥.) mix it thoroughly with 20 f℥. or 600 cc. of water, and allow the mixture to macerate over night. The water should be added to the powder in small portions with active stirring until a uniform smooth paste is made. The remainder is then added at once and the whole well stirred. A strong stirrer with a spatula-shaped, or spade-shaped end is almost indispensable to the convenient management of this process throughout. It is better to use this large proportion of water at the outset, because it enables the air to separate easily and well from the powder, and thus much improves the effect of the subsequent percolations;—because it forms a solution so dilute as not to be precipitated by subsequent admixture with the weaker percolates; and because it very much facilitates the final exhaustion of the residue. The powder continues to absorb tbe water, and the mixture to diminish in volume for several hours after the mixing.

Take two 9 inch or No. 22 round filters, fold them separately twice in the usual way for plain filters, and open them in the usual way, with one thickness of paper on one side and three thicknesses on the other. Then introduce one folded filter into the other in such a way that the three thickness side of each shall coincide with the one thickness side of the other. This double filter will then have four thicknesses of paper all round, and its effect in percolation is much improved by conducting off the liquid with uniformity in all directions. Place this double filter not too low down in a 5 inch or 12 centimetre funnel, and wet it well by filling the filter and funnel with water for a few

moments. Empty and drain the funnel and filter and place them on a proper funnel stand. Arrange a 16 f℥ or 480 cc. tared capsule or evaporating dish upon a water bath over a gas flame or other sufficient source of heat, and heat the water in the bath to boiling. Place the funnel stand so that the point of the funnel is over the capsule on the bath, and then having stirred up the opium mixture well, fill the filter from it, very nearly up to its edge, and continue to refill it occasionally until the whole of the mixture has been poured in. When the residue in the filter is drained, measure off 6 f℥. or 180 cc. of water, and rinse the vessel which contained the opium mixture two or three times with small portions of this water, dissolving off, or loosening whatever may have become adherent to the vessel by drying, by means of the stirrer, and pour the rinsings one after another into the top of the residue in the filter. Then keep the filter filled up with the remainder of the water until it has all been poured on, and again drain the residue. Then return the residue from the filter to the vessel in which the mixture was made, by the use of the spade-ended stirrer, leaving the filter as clean as possible, and unbroken in its position. To the residue add 1·67 f℥. or 50 cc. of water, stir it well into a smooth magma, and pour it back into the filter, draining and scraping as much of it out the vessel as practicable. Level it down in the filter, or rather so spread it out against the side of the filter as to leave the surface concave. Then measure off 5 f℥. or 150 cc. of water, and rinse the mixing vessel with small portions of this at a time until the vessel is clean, pouring the successive rinsings into the concave surface of the residue in the filter, and keep the filter filled up with the remainder of the water until it is all poured on. When the residue is drained, the filters and residue may be removed from the funnel, be flattened a little upon a folded newspaper, be put to dry, and when as thoroughly dried as the powdered opium was, may be weighed if desirable. In weighing, the outside filter is to be removed and placed in the weight scale to counterbalance the other one, or, if a nice weighing of the residue be desired, the inside filter must be weighed and the weight marked on it with lead pencil before it is used. The dry residue from good powdered opium weighs

about 736 grains or 47·7 grammes. If it be not desired to weigh the residue it is simply thrown away. If the water bath be well arranged, the evaporation of the percolate will be as rapid as its passage through the filter, even if a pretty thick porcelain dish be used. But if a tinned iron or tin capsule be used, the rate of evaporation will exceed that of the filtration, and the capsule will never get more than half full during the process. Stirring is not needed during the evaporation. The filtration and evaporation require from two to three hours. When the residue is drained and disposed of, set the hot capsule and contents on a scale, weigh them and subtract the tare of the capsule. It will commonly happen that the extract weighs less than the original weight of the powdered opium; if so, add water to it until it weighs the 1543 grains or 100 grammes. Then return the capsule to the water bath and warm the contents with stirring until the whole of the extract which has dried upon the capsule is entirely redissolved. Set the capsule on the scale and again add water to make up the loss by evaporation during this dissolving the extract. Return the capsule to the water bath again, and add to the contents 6 f℥. or 180 cc. of stronger alcohol, stir the mixture till it is uniform, and heat it to boiling. Clean the vessel used for the first mixture of the opium and water, and put into it 12 f℥. or 360 cc. of stronger alcohol, and while stirring this actively pour slowly into it the contents of the capsule. Rinse the capsule with 1 f℥. or 30 cc. of stronger alcohol, and add the rinsings to the main portion. Then cover the vessel to prevent unnecessary loss of alcohol by spontaneous evaporation, set it aside for 12 hours, or over night, and then pour off the clear alcoholic solution from the solid tarry residue. The first portion of alcohol added to the warm watery extract in the capsule is not sufficient to cause a precipitate, but is intended only to so dilute the extract as to render the after precipitation more perfect. The pouring of the contents of the capsule into the alcohol causes an immediate precipitation of a black tarry matter which collects upon the stirrer and vessel; but the solution does not become clear at once. That is, the precipitation is not complete for several hours. The first extraction of the opium by water rejects all the solid mat-

ters, all the resinous matter, much of the narcotin, and in short everything not soluble in water. But the gummy mucilaginous matter and nearly all the coloring matter is soluble in water, and forms a large and embarrassing portion of the watery extract. All the gummy matter and much of the coloring matter are insoluble in strong alcohol, and these constitute the black tarry matter precipitated when the watery extract is diluted and poured into the alcohol. This is the putrescible, fermentable portion of the extract, and its proportion varies greatly with the quality of the opium, being rarely less than 10 or 11 per cent. and rarely greater than 18 per cent. This tarry precipitate contains a small proportion of the useful alkaloids, entangled and carried down with it, and the larger the proportion of this tarry matter the more of the useful alkaloids it will contain. In one instance it was found to contain 0·6 per cent. of the weight of the original opium of morphia. If the precipitation be well managed, however, and particularly if time be valuable, the tarry matter does not contain enough alkaloids to repay the extraction until this residue saved from several operations shall have accumulated. But whether worked singly or accumulated they are dissolved in a little water by warming, the solution diluted with cold water until a filtered portion is no longer made turbid by farther dilution. The solution is then filtered off and the filtrate evaporated on a water bath to the consistence of a very thin extract. About ten times its volume of stronger alcohol is then added gradually, heated to boiling, set aside over night to again precipitate the now clean tarry matter, and then the alcoholic solution is poured off clear, and added to the larger portion of clear alcoholic solution poured off from the first precipitation.

The alcoholic solution is then put into a small tared still and, by means of a water bath, distilled until the alcohol is all over. By a good distillatory apparatus about four-fifths of the alcohol is thus recovered in a more dilute condition than when taken. This, by shaking with about one-eighth of its weight of powdered quick lime and redistilling, is again fit for the same use.

To the extract of opium in the tared still, after distilling off the alcohol, add sufficient water to make up the weight to 1543

grains or 100 grammes, or the original weight of the opium, and warm it in the water bath until the extract is completely dissolved. Then pour this solution into an eight ounce bottle, and rinse the still with a few drops of water, adding the rinsing to the contents of the bottle. When the bottle and contents are cold pour on to the diluted extract 3 f℥. or 90 cc. of stronger ether, stop the bottle well, shake it vigorously, allow it to stand a few moments till the ether separates, and pour this off as closely as is possible with care. Pour on 3 f℥. or 90 cc. more ether, again shake vigorously, and pour it off as closely as possible. Repeat this washing with ether a third time, when the accumulated washings will measure about 8 to 8·5 f℥. or 240 to 255 cc. Put this into the still and distil it to dryness in a water bath with great care, remembering the inflammability of the ether vapor. In this way about 7 f℥. of 210 cc. of the ether may be recovered in a condition to be used again for the same purpose. The residue from the ether washings varies very much in different parcels of opium, but may average about 1 per cent. of the weight of the opium. It is always a mixture of dark oily matter of a nauseous disagreeable odor, and a mass of solid matter which is amorphous or crystalline according to the rate of evaporation and the amount of heat used. By spontaneous evaporation large square tabular crystals are formed. Pour the diluted extract of opium, with the shallow stratum of ether which could not be poured off, from the bottle into the evaporating dish, and by means of the water bath evaporate it to about one half its volume. Put 10 f℥. or 300 cc. of water into the cleansed vessel first used for mixing the opium and water, and pour into this the contents of the evaporating dish, rinsing the dish with a little water, and adding the rinsing to the larger portion. This dilution produces another insoluble precipitate, but one which is loose and flocculent and easily washed on a filter. At this point it is necessary to decide whether the solution is to be made up or finished by weight or by measure, though it may be done by both, the weight answering as a check upon the measure, and *vice versa*. As it is always given by measure, (drops or minims) and has its formula constructed upon minims or volume;—and as different parcels of opium yield the

depurated solution of different densities, it would seem only proper to make it up by measure. But the measures usually accessible are so much less accurate than the weights that they cannot be relied on. Beside, the broad surfaces of measures are not calculated to give that degree of practical accuracy required now a days in adjusting potent medicinal agents. Under these circumstances measures and weights applicable to the average grades of opium will both be given, even at the expense of complication. But the operator who may have a set of weights which agree tolerably among themselves is advised to use these in preference to measures.

Take a tared flask marked in the neck to hold 17 fʒ, or 510 cc., (a common French or German half litre flask which is marked low in the neck answers well,) filter the opium solution into it, and wash the filter and residue through with a little water. To this solution add 1574 grains or 102 grammes of stronger alcohol, and, having agitated the mixture, add water until the whole weighs 7870 grains or 510 grammes. This 1574 grains or 102 grammes of alcohol, measured at a temperature of about 17° C. = 62·6° F., measures 4 fʒ and 48 ♏, or 123 cc., but when this is mixed with the watery solution there is a contraction of volume in the mixture equal to about 162 ♏, or 10 cc, and an increase of temperature of 3 or 4° C. = 5·4 or 7·2° F. When the mixture is made up to the 7870 grains or 510 grammes it will measure more than the 17 fʒ, or 510 cc., on account of the rise of temperature. When, however, it is cooled to the original temperature at which the liquids were when mixed, the measure will commonly be but a small fraction over or under the measure, as the opium contains more or less extractive soluble in both water and alcohol. This 7870 grains or 510 grammes of solution now contains 20 per cent. of its weight and 30 per cent. of its volume of the stronger alcohol; and is about the density of water,—that is 1 cc. at 17° C. weighs about 1 gramme. It is perfectly clear, and will remain so indefinitely, as it contains alcohol enough to prevent any change even in the warmest weather. It is now ready for assay, and should be kept in a bottle to prevent loss by evaporation while waiting for the result of the assay.

The process of assay consists simply in precipitating the morphia from an aliquot part of this solution by means of ammonia, —drying and weighing the morphia, and applying the result, by multiplication, to the remainder of the solution, so as to ascertain the quantity of morphia which this contains. By this, of course, the farther dilution and adjustment are made. Although this process of assay does not pretend to be critically accurate, yet it will be so in proportion to the care and nicety with which the different steps are followed as now to be described; and whilst without any extraordinary degree of skill it may be so conducted as to indicate within three or four tenths of a per cent. of the morphia value of the opium used, it can hardly be so mismanaged as not to come within one per cent. of the true value.

Take one-seventeenth part, or 463 grains = 30 grammes, or about 1 f℥, =30 cc. of the solution, and put it into a small tared capsule, and set the capsule in a saucer or plate which contains a shallow stratum of, or is about half filled with, water. Then make a mixture of equal parts of officinal water of ammonia and stronger alcohol, and take of this mixture about 77 grains or 5 grammes, or 5 cc., rather more than less,—and add it to the contents of the capsule. Stir the mixture and then cover the capsule with a large beaker or other glass vessel, inverted so that the edge of the beaker or vessel rests on the saucer or plate in the water, and allow the whole to stand at rest during two days or thereabouts. If there be no alcohol added to the water of ammonia, it will sometimes precipitate a portion of the morphia at once, and with it an undue proportion of coloring matter. When diluted with alcohol and in a somewhat alcoholic solution the morphia goes down gradually and slowly in the form of a crystalline crust of a chestnut-brown color, which adheres to the bottom and sides of the capsule. The precipitation is generally complete in 24 hours, often in 12 hours, but is occasionally retarded by unknown causes. It rarely increases after 48 hours, however, and this period is fixed in order to render the result pretty secure. The quantity of ammonia used may vary considerably without materially affecting the result. The quantity indicated is quite enough for opium of the best quality, but

it may be increased one-fourth, or even one-half without much disadvantage. The morphia thus precipitated is not pure, but contains coloring matter enough to give it a light brown, or a chestnut-brown color. The quantity of coloring matter present is, in weight, surprisingly small, and is fully counterbalanced by the small proportion of morphia which refuses to crystallize out. The results are therefore pretty accurate, or at least practically accurate. If the little capsule with the assay be allowed to stand merely covered with paper or a watch-glass for the 48 hours, some of the solution will evaporate away, and form a hard ring of dried extractive matter upon the capsule all round the edge of the liquid, and this would be subsequently weighed as morphia. A pellicle forms on the surface too, and in whole or in part remains in the capsule when the mother liquor is poured off. By the simple device of covering the capsule, and preventing all change of air by a water joint, as described, all this inconvenience is avoided. And beside, the water absorbs the vapor of ammonia as the excess of this precipitant is given off from the solution, and diminishes this excess about as well as if the capsule was left exposed for it to fly off. At the end of the 48 hours the mother-liquor is poured off clean from the adherent crust of morphia which lines the capsule, and the capsule is supported on edge upon some folds of bibulous paper for half an hour to drain. It is then put in a larger capsule on the water bath for an hour to dry, when it is ready for weighing. This weighing should be done on a scale sensitive to about the eighth or the fourth of a grain, and with good weights of course. The capsule and contents are weighed, and the tare or weight of the capsule is subtracted; and the weight of morphia thus ascertained will be in proportion to the quality of the opium. If the powdered opium be within the officinal limit the morphia will weigh not less than 7·72 grains or 0·5 gramme, but it may weigh anywhere between this and say 15·4 grains or 1 gramme. Now as the whole of the solution represented the whole of the opium, and as one-seventeenth of the solution has yielded a quantity of morphia which is now known, it is only necessary to multiply this quantity by 17 in order to know what the whole solution would have yielded if precipitated in this way; or to

multiply it by 16 to know how much morphia the remaining sixteen-seventeenths of the solution contains. Suppose the morphia in the capsule to weigh 11·42 grains or 0·74 gramme. Then 11·42 × 17 = 194·14, and the 1543 grains of powdered opium taken contained 194·14 grains of morphia. Then, as 1543 : 194·14 : : 100 : 12·58 = the percentage of morphia in the opium. Or, it weighs 0·74 gramme. Then 0·74 × 17 = 12·58, and the 100 grammes taken contained 12·58 grammes of morphia. Then, as 100 : 12·58 : : 100 . 12·58 = the percentage of morphia in the powdered opium. But there is only sixteen-seventeenths of the solution remaining, and the other seventeenth part in this supposed case has given 11·42 grains or 0·74 gramme of morphia. Therefore, this quantity multiplied by 16 would give 182·72 grains or 6·04 grammes as the whole quantity of morphia in the remainder of the solution.

This is by no means the only process of assay well adapted to this purpose, and perhaps not the best one. Any of the ordinary morphiometrical processes are good enough, and here, as in most chemical processes, that one is best to which the operator is best educated, and with which he has most experience. A practice of nearly twenty years, growing out of the old Staples process for the extraction of morphia, has led the writer to place a good deal of confidence in this plan; and though it does not pretend to critical accuracy, it is doubtful whether any process that is more complex, more difficult, or more critical, would be adapted to the present condition of pharmacy. Pharmacy should not pretend to be chemistry, and results in this direction which may be far short of chemical accuracy would be an important advance for pharmacy. Simple and easy processes of assay are alone applicable to pharmacy, and the practice of such soon leads to greater accuracy in these first, and then to more accurate processes. This process of assay is easily applicable to powdered opium, and gives results the accuracy of which is proportionate to the dexterity with which it is applied. If a parcel of powdered opium is to be assayed by this process, it is only necessary to take 10 grammes = 154·3 grains, instead of 100 grammes = 1543 grains, and then to divide the whole detail as given by 10. Indeed, the whole detail given is but the writer's process of assay

for opium multiplied by 10, and to him it appears both simple and easy, and has often been verified by extractions of morphia on the large scale by various processes.

Now it is probable that the average yield of morphia from good powdered opium now-a-days will not be over 10·5 to 11 per ct. And the officinal tincture, containing 1·25 troyounces or 600 grains of such opium to the pint, would therefore contain 63 to 66 grains of morphia to the pint. Hence 64 grains of morphia to the pint, or 4 grains to the fluidounce, is assumed as the standard of strength of the officinal tinctura opii, or laudanum.*

This assumed strength for the officinal tincture has always been used as the standard of strength for liquor opii compositus, and will continue to be so.

It is therefore only necessary to divide the number of grains of morphia contained in the remaining sixteen-seventeenths of the depurated solution by 4, in order to obtain the number of fluidounces of 30 cc. each, to which the solution must be made up when finished for use. In the supposed case the 182·72, or say 183 grains, divided by 4, gives 45·75 fluidounces, or 1372 c.c., as the measure for the finished solution.

Now if it be desired to make the simple liquor opii, as suggested on page 5, it is only necessary to add water and alcohol in the quantities indicated by the assay, keeping the proportion of alcohol as small as may be with safety. With one-sixth of its weight of alcohol the preparation would probably keep indefinitely, and could then be used by hypodermic injection.

When the solution is to be made into liquor opii compositus, the proceeding is less simple.

Thirty cubic centimetres or a fluidounce of the preparation, when carefully and accurately made on the basis given on page 7, weighs from 28·95 to 29·05 grammes, or from 446·76 to 448·30 grains, varying to this extent only when made from different parcels of good, and only fair quality powdered opium. Twenty-nine grammes, or four hundred and forty-seven and a

* Morphia ($\overline{Mo}$ = 303) is to crystallized sulphate of morphia ($\overline{Mo}$, SO_3, $6HO$,=379) as 303 is to 379 or thereabouts, and therefore 4 grains of morphia is about equivalent to 5 grains of crystallized sulphate of morphia.

half grains, is therefore adopted as the standard weight of thirty cubic centimetres, or one fluidounce of a properly made preparation, measured at 17° C. = 62·6 F.

This would indicate the following composition or formula for each 30 c.c. or 1 fluidounce of liquor opii compositus:

Depurated solution of opium containing,—

4 grs. morphia,	14 c.c. = 15·047 grms.,	= 232·17 grs.	= 51·887 p.c.
Stronger alcohol,	13 c.c. = 10·686 "	= 164·91 "	= 36·848 "
Purif. chloroform,	1 c.c. = 1·499 "	= 23·13 "	= 5·169 "
Acetic ether,	2 c.c. = 1·768 "	= 27·29 "	= 6·096 "
	30 c.c. = 29·000 "	= 447·50 "	= 100·000 "

When it shall have been determined by the assay how many fluidounces of the finished preparation the solution will yield, this number of fluidounces is to be multiplied by 447·5, or the number of grains in each fluidounce when finished, and the product will be the weight in grains of the finished preparation. This number of fluidounces multiplied by 164·91, or the number of grains of alcohol in each finished fluidounce, will give the weight in grains of the whole quantity of alcohol required. But a constant quantity of 1574 grains of the alcohol is required in, and has already been added to the watery solution before the assay, and therefore this quantity must be subtracted from the whole quantity required, and the remainder, only, must be taken for the final adjustment. This same number of fluidounces of the finished preparation multiplied by 23·13, or the number of grains of purified chloroform in each finished fluidounce, will give the whole weight in grains of chloroform required. The same number of fluidounces of the finished preparation multiplied by 27·29, or the number of grains of acetic ether in each finished fluidounce, will give the whole weight in grains of acetic ether required. These calculations are really simple, and may be usefully illustrated by continuing the supposed case taken to illustrate the application of the assay.

The 182·72 grains of morphia found to be in the remainder of the solution assayed (the 16 fluidounces or 480 c.c.), divided by 4, gives 45·75 fluidounces or 1372 c.c. as the measure for the finished liquor opii compositus when it shall contain the required

four grains of morphia in each fluidounce. Then 45·75 fluidounces multiplied by 447·5 grains, the weight assumed for each fluidounce of the finished preparation, gives 20473·125 grains, which is the weight to which the solution must be made up in finishing it. Then 47·75 × 164·91 = 7544·63, which is the whole number of grains of alcohol to be contained in the finished preparation. But the constant quantity 1574 grains of alcohol has already been added before the assay, and therefore this must be subtracted from the whole quantity. Then 7544·63—1574 =5970·63, which is the number of grains of alcohol still required to finish the preparation in this supposed case.

This latter quantity is weighed into a tared bottle which will hold the entire finished preparation.

Then 45·75 × 23·13=1058·20, which is the number of grains of purified chloroform required. This is weighed in any convenient vessel, and poured into the bottle containing the alcohol. Then 45·75 × 27·29=1248·52, which is the number of grains of acetic ether required. This is weighed in the vessel used for the chloroform, and is also poured into the bottle with the alcohol. The bottle is then shaken to mix the contents, the assayed opium solution added, and the bottle again shaken. This remainder of the assayed opium solution weighed 7407 grains, and consisted of 5926·6 grains of watery solution and 1481·4 grains of alcohol. It originally weighed 7870 grains, and consisted of 6296 grains of watery solution and 1574 grains of alcohol, but 463 grains of the mixture (370·4 grains watery and 92·6 grains alcohol) was taken for assay. The bottle now contains of

Assayed opium solution,	7407·00	grains.
Remainder of the alcohol,	5970·63	"
The chloroform,	1058·20	"
The acetic ether,	1248·52	"
Making,	15,684·35	"

But it is required to weigh 20,473·125 grains, and this weight is to be made up with water. Therefore, 20,473 grains less 15,684 grains gives 4789 grains as the quantity of water required to complete the weight and finish the process.

Leaving the completed illustration now, and resuming the

formula: Take a tared bottle of sufficient capacity to hold the finished preparation, and having weighed into it in succession the remainder of the alcohol required, the purified chloroform and the acetic ether, shake them together and then add the opium solution. Then set the bottle on a scale, and having carefully adjusted the weights to the required complete quantity, add water until this quantity be made up, and shake the mixture. Upon first adding the water the mixture becomes cloudy and suffers contraction and consequent rise of temperature, and if measured now, to control the weighing, the measure will be found plus. But after standing over night, the measure should be found pretty nearly accurate, if the measures used be good. The French litre and half-litre flasks, and a pipette graduated upward in cubic centimetres to 30 or 50 cubic centimetres, are not only extremely useful in this process, but also for many uses, and particularly for testing the accuracy of graduated measures.

When the completed preparation is well shaken, the cloudiness disappears, and it gives a clear bright solution of a deep brownish or yellowish garnet color, and having a rather oily fluidity as it drains down the sides of a glass vessel. The taste is sweet, pleasantly aromatic and somewhat pungent at first, but soon passes to a peculiar, not intense bitterness—the bitterness being that of other opium preparations, but less intense, less disagreeable, and less persistent, and comparatively if not wholly free from the nauseous quality of the opium bitterness. The odor is a refreshing agreeable admixture of the acetous pungency of the acetic ether and the sweet pungency of the chloroform, and recalls that of the vinaigrette smelling-bottle used as a restorative by the ladies. It is miscible in all proportions with alcohol, water, wine, syrup, etc., and is thus well-adapted to compounding in prescriptions. It is perhaps best given in water, the quantity of water being varied at pleasure, but generally limited to the smallest convenient quantity—say, a teaspoonful or a tablespoonful of ice water to each dose. When first mixed with water the mixture is cloudy, but this cloudiness is only momentary.

The dilution, and the irritant action of the chloroform, acetic ether, and the large proportion of alcohol, interfere materially with its application by hypodermic injection. The old liquor

opii compositus was badly adapted to this mode of administration, but was still often so used. This new formula is, however, much less applicable to use in this way. It may, however, be rendered applicable in precisely the same way not unfrequently adopted with the old preparation, namely: by exposing a weighed small quantity at a time, in a shallow vessel in a warm place, until the weight is reduced to one-half or one-third. If reduced to one-third, it will be about the strength of the solution of sulphate of morphia called Magendie's solution; but it will then have too little alcohol to keep longer than a few weeks. If reduced to one-half, the chloroform and acetic ether and much of the alcohol will pass off sufficiently, and yet leave enough alcohol to preserve it. If the alcohol be all or nearly all driven off, the effect of very dilute solutions of phenol, or the so-called carbolic acid, in protecting solutions for hypodermic use from change, may be resorted to. All solutions for such use should be perfectly clear and bright, either by settling or by filtration, and should be carefully guarded against decomposition, since many of the accidents which occur in hypodermic medication are probably caused by the introduction of liquids which are undergoing change, or by inoculation from a badly kept or imperfectly cleaned syringe point.

The compound solution of opium evaporated on a water bath to one-fourth its weight or less, then diluted to one-third its original weight with water, and, when cold, filtered, will give the best solution for hypodermic use. But the coloring and extractive matter is objectionable for this use. If such a solution is to be kept even for a few days (and no hypodermic solution should ever be kept long), it may be protected by the addition of about one-fiftieth of its weight of an alcoholic solution of phenol (crystallized carbolic acid) containing two per cent.

In conclusion, it may be remarked in connection with this liquor opii compositus, as in regard to other agents which are liable to become hobbies, that perhaps the greatest skill in using it is to know when to prefer something else.

Brooklyn, Dec. 15, 1869.