VIII.—*On Microscopical Research in relation to Pharmacy.*

By Henry Deane, F.L.S., and Henry B. Brady, F.L.S.

[Read at the Bath Meeting of the British Pharmaceutical Conference, Sept., 1864.]

We have chosen for the particular subject of the present communication the various preparations of opium. Whether regarded in respect to their importance in the practice of medicine, their variability in strength and character, or the peculiar conditions in which the active matter exists in the crude drug, no better subject could be found for the purpose in view.

Opium, as is well known, is an extremely composite substance, being a pasty mass formed of resinous, gummy, extractive and albuminous matters, containing a larger or smaller percentage of certain active principles diffused through it. These principles are morphine, narcotine (with its two homologues), codeine, narceine, meconine, thebaine, and papaverine, either existing free or in combination with meconic, sulphuric, or other acids, the sum of the crystalline constituents, exclusive of inorganic salts, contained in good samples of the drug, being from twenty to thirty per cent. of its entire weight. Any preparation, exactly to represent opium, must contain the whole of these principles, as indeed the tincture may be said fairly to do.

It has, however, been shown that some of the principles are inert, and others even deleterious in their action, and we have consequently had a class of preparations introduced which are understood to be of superior efficacy, not from their containing any active matter which the tincture does not contain, but because they are free from certain substances which are retained by it. Narceine, meconine, and meconic acid are believed to be inert, whilst narcotine possesses properties widely different from those for which opium is usually employed. Of the bulkier constituents, the resin appears to be worse than useless, whereas the bitter extractive, though opinions differ with regard to its precise properties, seems at any rate to increase the narcotic power of the more active constituents. A typical preparation of opium should therefore at least contain the whole of the morphine and codeine, with meconic or some other acid to keep them in solution, and the bitter extractive. Codeine itself, and the salts of both codeine

and morphine, are readily soluble in either water or alcohol; the remaining principles are fully dissolved by alcohol, but scarcely soluble in water; hence, in the preparations alluded to, water rather than alcohol is used as the solvent.

The process we adopt in examining the constituents of a fluid preparation of this sort under the microscope is a very simple one.

Having, as a preliminary step, taken the specific gravity, and ascertained the percentage of carefully dried extract contained in it, we evaporate a small quantity, usually from four to six drachms, on a sand-bath in a watch-glass, to about the consistence of treacle. It is then poured upon a slip of glass and covered with a piece of thin glass, and after standing a few days, it is sealed in with gold-size. Crystallization sometimes commences before the preparation is removed from the watch-glass, sometimes immediately after transferring to the glass slip, but in many cases not for several days. The time taken is dependent on one of two influences, viz., the quality of the opium, and the exact degree of inspissation.

In determining the value of a preparation from the appearance of this extractive under the microscope, we do not rely entirely upon the amount of crystallization; it is requisite to go one step further to obtain the full value of our labour, and by investigating the form and physical characters of morphine and its compounds, of codeine, narcotine, meconic acid, &c., place ourselves in position to see the significance of the appearance the slide exhibits, and to identify any crystalline principles which may be present. Nevertheless, even in the absence of very accurate knowledge, any one who will make a few experiments for the sake of practice will soon be able, by observing the presence or absence, the abundance or scarcity, of certain forms of crystals easily seen in typical specimens, to pronounce with little hesitation on the quality or genuineness of samples of any of the ordinary preparations of opium.

Before proceeding to speak of the opiates which have come under our examination, it may seem necessary to say a few words on the forms assumed by the various opium principles and the physical characters their crystals present. This, together with certain drawings we have made carefully from specimens, will afford a key to our further remarks.

In the first place:—

Morphine.—The pure alkaloid crystallizes in right-rhombic prisms

often running into needles. The single crystals have but little effect upon the polarized ray, but where the solution has been concentrated (as from alcohol), and the acicular crystals are much overlaid, they present a good deal of colour. (Plate I, fig. 1.)

It is exceedingly difficult to say in what condition morphine exists in opium; we are well aware that it has been set down as meconate, with a smaller percentage of sulphate, but we have reason to suspect that sulphate is present to a larger extent than is generally supposed. The messing and manipulation which all kinds of opium appear to undergo before they reach this country, renders the belief which is suggested by other circumstances, that a portion of the meconic acid is decomposed, extremely probable. It is scarcely likely that a substance which even boiling water decomposes, with evolution of carbonic acid, should remain unchanged through the various treatments to which the drug is subjected.

Meconate of Morphine is set down in chemical works as being uncrystallizable, a statement to be accepted with reservation; for by careful manipulation peculiar conical crystals may be obtained either from the solution of the commercial salt in dilute alcohol (Plate I, fig. 3 *b.a.*), or by the evaporation of mixed solutions of morphine and meconic acid (Plate I, fig. 3 *b.b.*). These crystals do not resemble any that are found on evaporating opium solutions; but as we have said, the subject requires more investigation than we have as yet been able to give to it.

Sulphate of Morphine takes the form of small flat-ended prisms, with a strong tendency to collect in radiating tufts; only the larger flat crystals polarized (Plate I, fig. 3 *a*).

Codeine crystallizes in octahedra running into four-sided prisms. In the octahedral condition it is not easily mistaken for any other of the oplum-alkaloids, but the prisms strongly resemble those of narcotine. (Plate I, fig. 4 *a*).

They may be distinguished by their not presenting the fluted or striated surface which crystals of narcotine have, and by their much less striking effect on the ray of polarized light.

Narcotine occurs in the form of prisms, with oblique one-or two-faced ends. As above stated, the surface of the crystals is fluted or striated, and on pressure they break up into tolerably regular smaller crystals (Plate I, fig. 2). Owing to a sort of composite structure, they have very marked effect on the polarized ray, more striking indeed than any other of the opium principles. Were it not for this property, they would be distinguished with great diffi-

culty from many other crystalline substances which they resemble in form. There is a tendency, as in other cases, to cluster together in more or less radiating tufts, but the individual crystals still keep their shape, and do not degenerate into mere radiating plumose needles, like those of narceine.

Narceine.—As narceine exists in opium in about the same percentage, on the average, as morphine and narcotine, it is of greater consequence in these investigations than it is in a medical point of view, being probably an inert substance. It is readily soluble in alcohol, and slightly so in water, and therefore must exist to considerable extent in most of our preparations. The absolute form of the individual crystals it is impossible to determine, but the masses of delicate, somewhat opaque, silky needles, either radiating from a centre or taking an irregular feathery shape, are very characteristic, and the absence of any effect on a ray of polarized light is a negative property of importance. (Plate I, fig. 6 *a*).

Meconine occurs in six-sided prisms with dihedral summits, and has little, if any, polarizing power. (Plate I, fig. 5 *a*).

Thebaine is readily soluble in alcohol, slightly so in water. From solutions in weak alcohol it crystallizes in beautiful rectangular plates, often associated in tufts more or less radiating from a centre. (Plate I, fig. 4 *b*). It is a most beautiful polarizing object.

Papaverine is present to so trifling an extent that it scarcely requires notice. The little which is dissolved by boiling water crystallizes out again on cooling in minute needles often aggregated in rounded balls, so closely packed as to be quite opaque. The large crystals obtained from the alcoholic solution possess slight polarizing properties (Plate I, fig. 6 *b*).

Meconic Acid.—Although the meconate of morphine in opium is an acid salt, it seems probable that part of the meconic acid is also there in a free state; at any rate, we frequently find it in preparations. As it is soluble in both alcohol and water, preparations are pretty sure to contain whatever quantity does exist in the crude drug, unless it has been removed by chemical means The form of the crystals is primarily a square prism, but we have only seen this in minute examples, and it is very difficult to trace the relationship to this type in the flat, pointed lozenges, somewhat resembling the attenuated forms of uric acid, which generally occur. Even these frequently run into still more strange varietal shapes, whose only resemblance to the lozenge-form exists

in their broad centres and two pointed ends (Plate I, fig. 5 *b*). They all have some effect on the polarized ray. Boiling water decomposes meconic acid; carbonic acid is given off, and comenic acid, a substance we have not yet studied, is formed.

We may now proceed to the practical application of the facts enumerated, and detail the results of the examination of the many preparations which have come under our notice.

Of *Turkey Opium* we have investigated—firstly, the tincture, prepared by ourselves from different samples of opium, as well as specimens procured from certain well-known operative chemists; secondly, the extract; thirdly, the wine; fourthly, the more or less aqueous solutions sold as Liquor Opii Sedativus, Battley's, one or two samples prepared by ourselves, and specimens procured from four well-known firms; and fifthly, certain proprietary opiates, viz., "Black Drop," "Jeremie's Sedative," "Nepenthe," and that sold as "Solution of Bimeconate of Morphia."

We have drawn careful figures of the appearances presented by the whole of these, which will do more than any description towards giving a correct understanding of the facts elicited; at the same time, it may be necessary to draw attention to some matters of importance in connection with them.

Tincture yields, on evaporation, crystals of almost the whole of the opium principles, and we find that, as the spirit volatilizes, the resin is also precipitated in an insoluble form. Our own preparation, from different samples of good opium, is tolerably constant (Plate II, fig. 1 *a* and *b*), and agrees in appearance with a specimen procured from a manufacturing house of some standing (Plate II, fig. 3); but neither are quite so rich in crystalline principles as a sample furnished to us by our friend Mr. Morson (Plate II, fig. 2), which seems to have been prepared from peculiarly fine opium.

Extract shows a much smaller proportion of narcotine crystals, with abundance of morphine salts and tufts of narceine (Plate II, fig. 4). Turkey opium is not rich in codeine, and we suppose that in extract prepared from it this principle is retained diffused through the bitter matter. A specimen of *commercial* extract of opium which we have seen, recently imported from the East, is a very different substance, showing fewer morphine crystals, but a large proportion of codeine (Plate II, fig. 5).

Wine.—The mucilaginous matter of wine very much retards, if it does not entirely prevent, the formation of crystals upon eva-

poration, and consequently we can say but little respecting the appearance presented by the extract obtained from vinous solutions.

Liquor Opii Sedativus.—The striking appearance resulting from the evaporation of Battley's Sedative (Plate III, fig. 1) first drew our attention to the mode of investigation now described. We have examined it frequently, and have always met with the same characters. The slides present an almost opaque mass of crystals of morphine-salts and codeine, with a very small proportion of narcotine (and meconic acid?), and, so far as we have observed, complete absence of resinous matter and narceine. Any one who has studied the microscopic characters of this preparation will readily understand how it has kept its place with the profession. We have necessarily thought much as to its probable mode of preparation, and cannot see any reason to doubt the statement made by Dr. Pereira, on the authority of the late Mr. Battley himself, that spirit and water were the only solvents used in its preparation from Turkey opium. Dr. Christison discredits the statement, on the ground of the comparative absence of meconic acid; but, as we have before said, boiling water is sufficient to decompose that acid, and therefore the argument is not a valid one. Though we have experimented much with a view to preparing a similar liquor, we have not yet arrived at an identical result. Plate III, fig. 2 *a* and *b*, shows two preparations with similar, perhaps nearly equal, sedative properties to the original fluid; but it will be seen they both differ considerably in the crystalline matters they contain. The preparation which gives results most nearly like Battley's of any which we have had opportunity of testing is that made by Mr. Morson, of London (Plate III, fig. 3). Of three other makes which we have examined, one (Plate III, fig. 5) is largely charged with resinous matter, and the proportion of crystalline constituents is so minute that we are satisfied its activity must be very small; another (Plate III, fig. 4) gives a few morphine crystals, a good deal of narcotine, and more narceine; a third (Plate III, fig. 6), is chiefly remarkable for its lack of everything crystalline.

There are certain preparations, to which we must next allude, which give little or no evidence as to the active matters they hold in solution by crystallization on evaporation. As examples, we may instance Vinum Opii, amongst officinal, and Braithwaite's black drop, Nepenthe, and a fluid sold as "Solution of Bimeconate

of Morphia," amongst proprietary formulæ. That there should be exceptional cases in which the reaction with a certain peculiar set of tests is doubtful, is only what might have been expected, and it can scarcely be regarded as a weak point in their application. Scarcely any *chemical* test we use but is open to some contingency of the same sort, but as long as we know the conditions of uncertainty it is no drawback to its employment; it only becomes necessary that these conditions should be investigated, and comparison becomes easy.

We have found that when opium is exhausted, the liquor evaporated to an extract, and this extract redissolved in alcohol, the tendency to crystallize is very much lessened or entirely destroyed. The cause of this we are not yet able to explain with certainty, but may state the fact as one which we have noticed in relation to every sort of opium we have worked upon. It will account for the very sparing indications of crystalline principles from all preparations made by redissolving in alcohol a once-formed extract. The residue not taken up by alcohol in the experiment is readily soluble in water, and contains certain crystalline matters which we have not yet examined sufficiently to report upon. Again, the subacid viscid matter left on evaporating wine prevents crystallization, consequently Vinum Opii gives a clear non-crystalline extract; we believe this also to be the reason why one of the proprietary preparations named yields the same result, as it seems to us to be a mere solution of morphine or one of its salts in wine, and not to be made direct from opium. The well known "black drop" gives no crystals upon evaporation, but in their place a peculiar deposit, consisting of an amorphous, almost opaque fæculence. This is probably owing, in great measure, to viscid matter held in solution, which on evaporation becomes insoluble through some change and is precipitated, carrying down with it the active matter. We know too little of the solvent employed to speak very positively, but if the commonly received theory be true,—that it is made by a fermentation process, in which impure malic acid is concerned,—we can readily understand how viscid organic matter may be present in sufficient quantity to produce the result alluded to.

In addition to the preparations of Turkey opium, we have also had the opportunity of experimenting on small quantities of the Patna, Malwa, and Persian varieties, and all of them present peculiarities of interest. An aqueous extract and a tincture have been

made from each, and from the Patna sort sufficient has remained to make a specimen of liquor.

The most striking fact in connection with the whole of them is the existence of large quantities of codeine. In the extract of Patna opium (Plate IV, fig. 1) it is the chief crystalline constituent, and though the liquor (Plate II, fig. 6) shows abundance of the other opium principles, it evidently owes its narcotic effect much more to codeine than Turkey opium does. We have the experience of an opium-eater on this point; he states that the quantity required to produce the effect is larger, but there is less discomfort in the after effects than with other sorts. Malwa opium (Plate IV, fig. 2 and 5) shows more narcine and narcotine, but in the tincture we have, in addition to a mass of minute crystals, certain larger prisms, which are probably codeine. Persian opium (Plate IV, fig. 3 and 6) also evidently contains a large proportion of narcotine and codeine.

We stated at the commencement that this must be looked upon only as a preliminary research, there remaining many points on which our information is far from complete. In continuing the inquiry we intend to devote ourselves chiefly to the elucidation of certain particulars. *Firstly*, the condition or form of combination in which morphine exists in crude opium; *secondly*, the relation of extract of poppy to opium in respect to crystalline principles; and *thirdly*, the influence which the extractive matters may have in altering the crystals obtained in opium solutions, and the variations of the normal forms induced by this cause.

The general conclusions we have arrived at in addition to a knowledge of the appearances presented by typical and special preparations of Turkey, Patna, Malwa, and Persian opiums are mainly these:—

That tincture, most nearly of any of the preparations, represents the properties, good and bad, of the crude drug.

That when crude opium is taken up with proof spirit as in tincture, the resin separates on evaporation.

That the preparations which have held their ground with the public and the medical profession, in spite of their cost, differ from the tincture in comparative freedom from resin and narcotine, and in containing only a diminished quantity of meconic acid.

That in the preparation of extract of opium it is important to use a large quantity of distilled water to ensure the separation of narcotine and resin.

That when extract of opium is dissolved in water, filtered, and evaporated again to an extract a second or third time, the crystals frequently differ considerably from those seen in the normal or first formed extract.

That when extract of opium is taken up with rectified spirit 56° O.P., and evaporated again to an extract, crystallization does not take place, or only to a very trifling extent.

That morphine and its salts, and perhaps other opium principles, do not crystallize readily from their solution in wine.

Finally, it remains for us to express our obligation to our friends Mr. Morson, of London, and Messrs. T. and H. Smith, of London and Edinburgh, for the courteous way in which they have assisted us with specimens, when working upon those of the alkaloids which exist only in minute quantities in opium; without this assistance we could scarcely have procured them in a state of reliable purity.

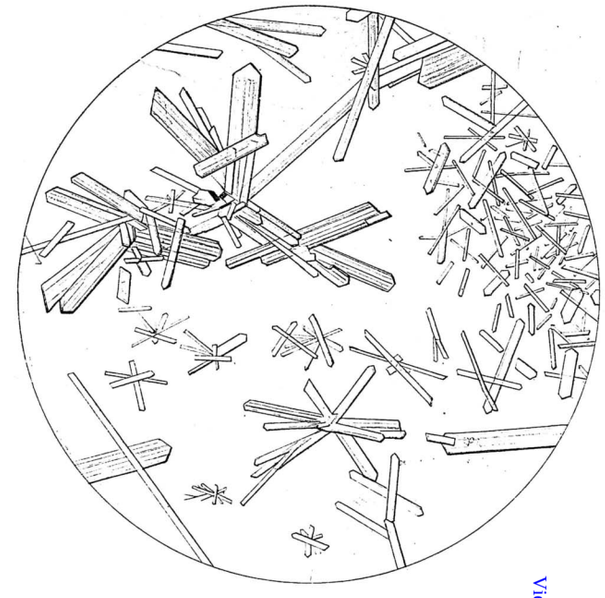
MICROSCOPIC APPEARANCE OF OPIUM PRINCIPLES.

PLATE 1.

FIG: 1.

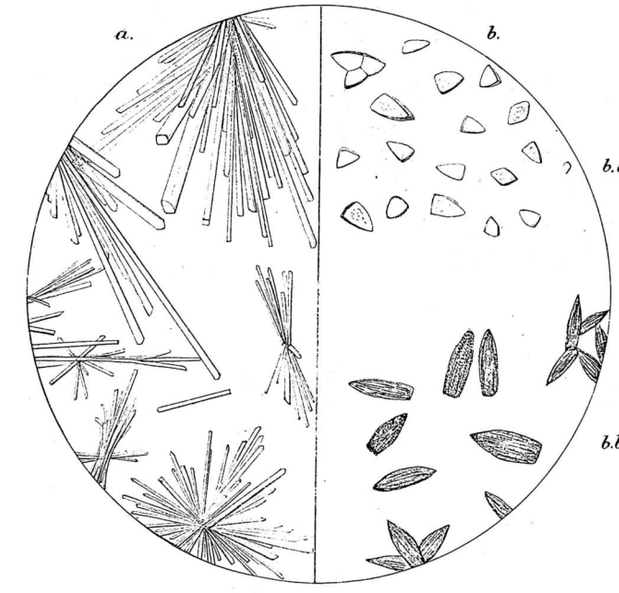
MORPHINE.

FIG: 2.



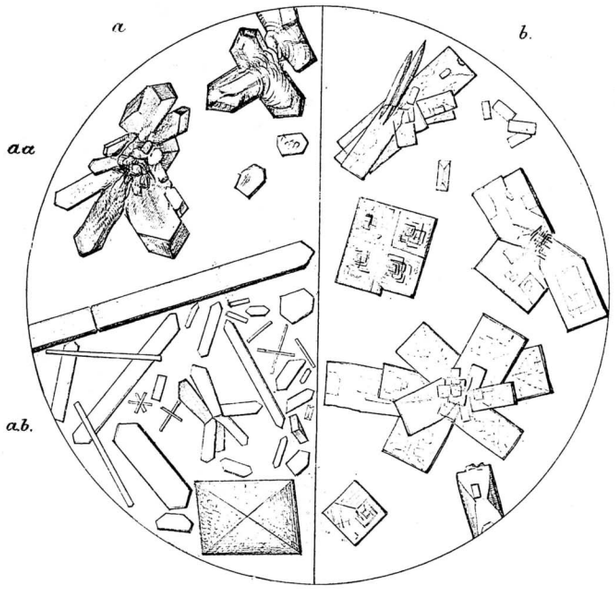
NARCOTINE.

FIG: 3.



SULPH. MORPHINE. MECONATE MORPHINE.

FIG: 4.

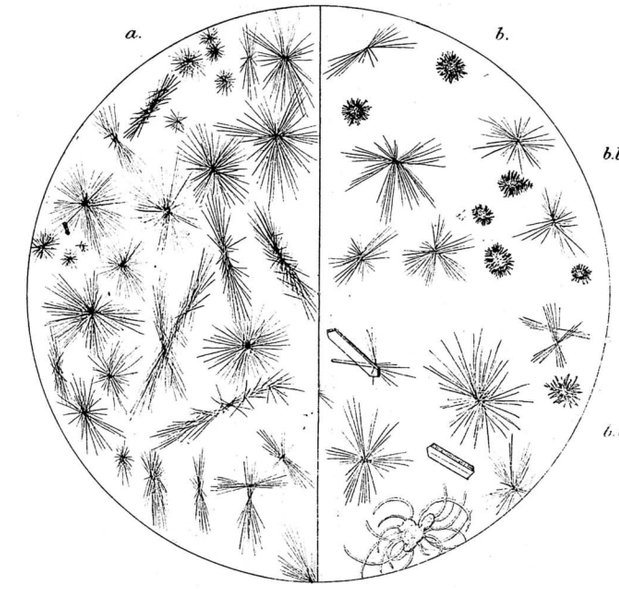


CODEINE. THEBAINE.

FIG: 5.

MECONINE. MECONIC ACID.

FIG: 6.



NARCEINE. PAPAVERINE.

H.B.Brady. del. ad nat

Tuffen West. sculp.

W. West imp.

LIQUOR OPII SEDATIVUS.
(TURKEY OPIUM.)

PLATE 3

FIG: 1.

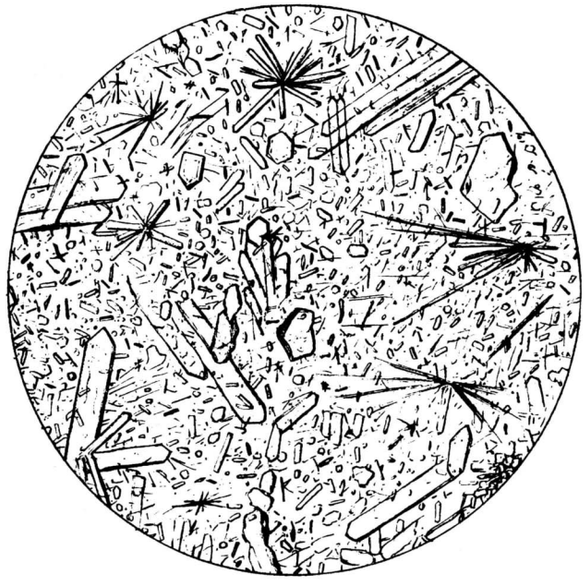


FIG: 2.

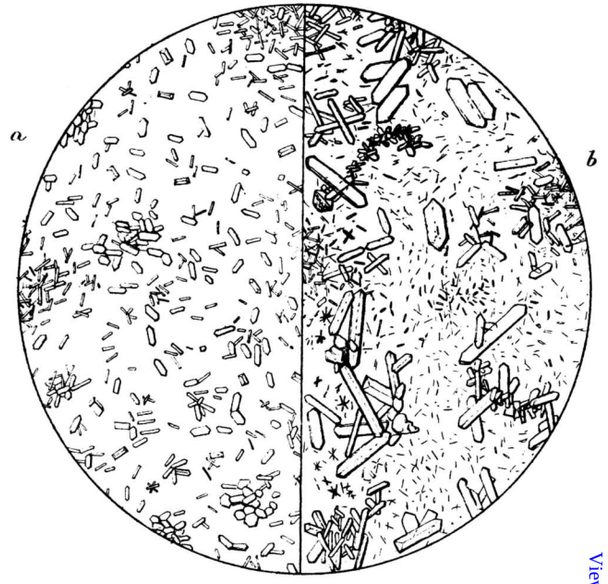


FIG: 3.

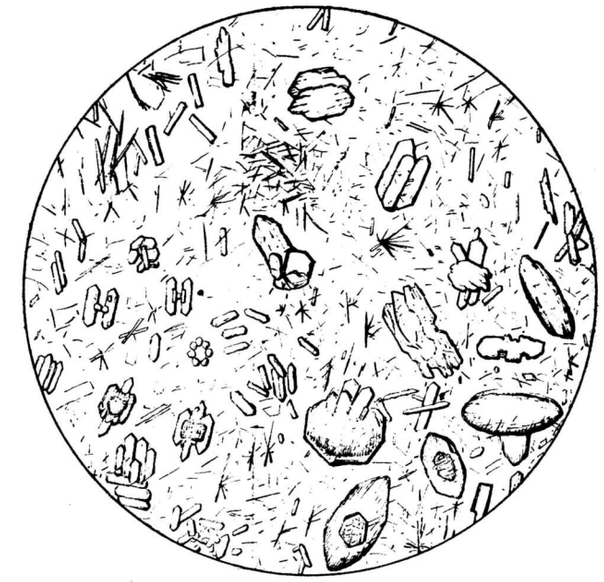


FIG: 4.

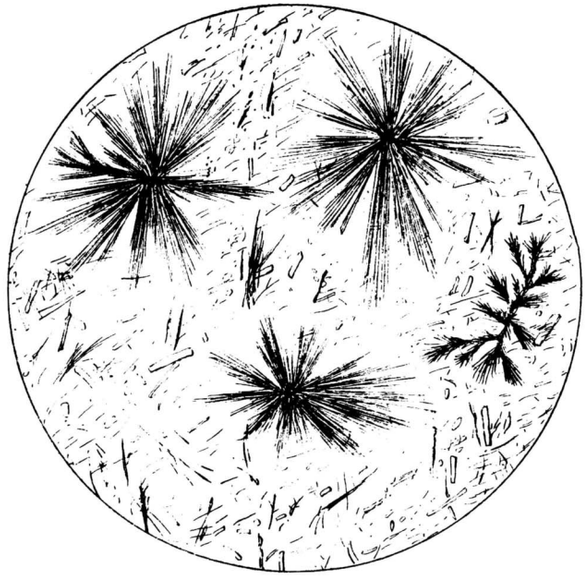
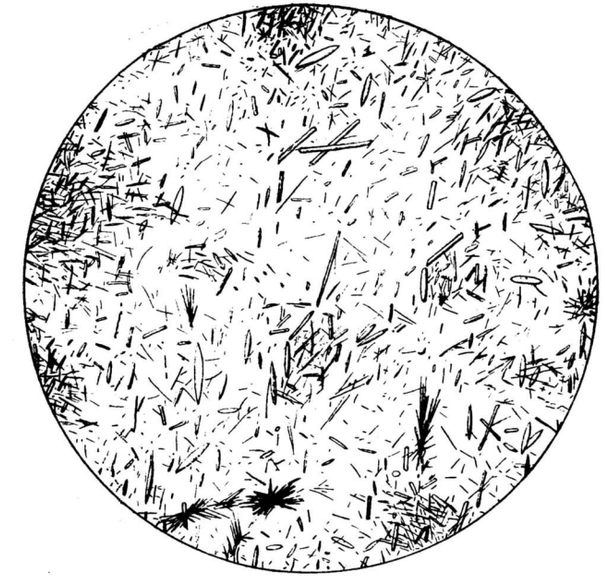


FIG: 5.

FIG: 6.



dy del ad nat.

Tuffen West, sculp.

W. West, imp.

TINCTURA OPII, &c.

PLATE 2.

FIG: 1.

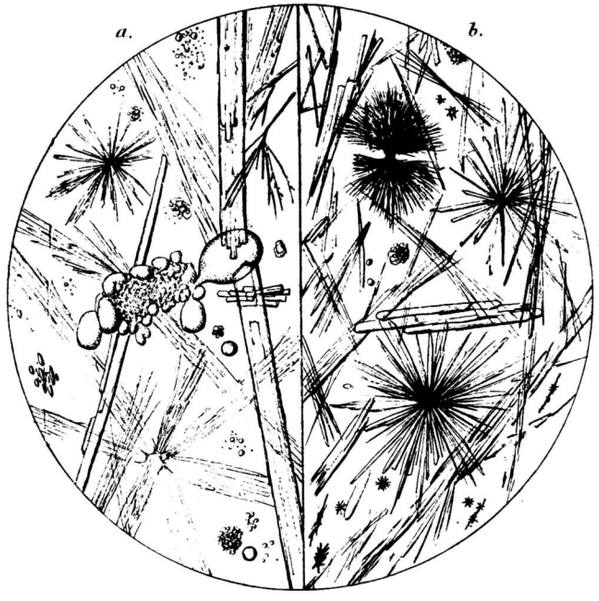


FIG: 2.

FIG: 3.

FIG: 4.

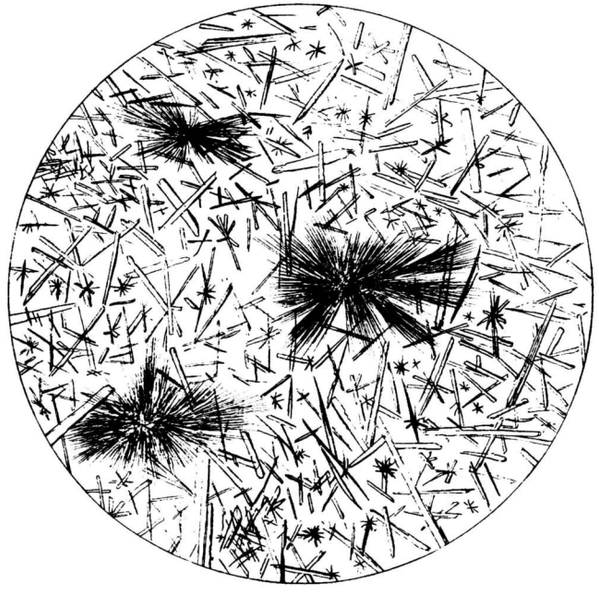


FIG: 5.

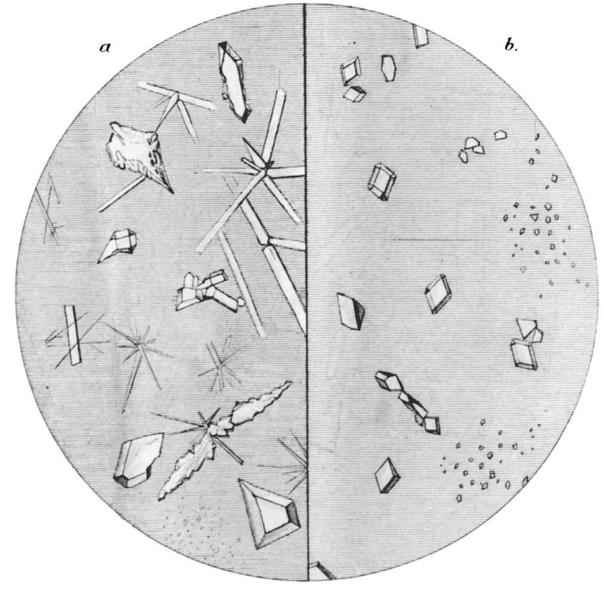
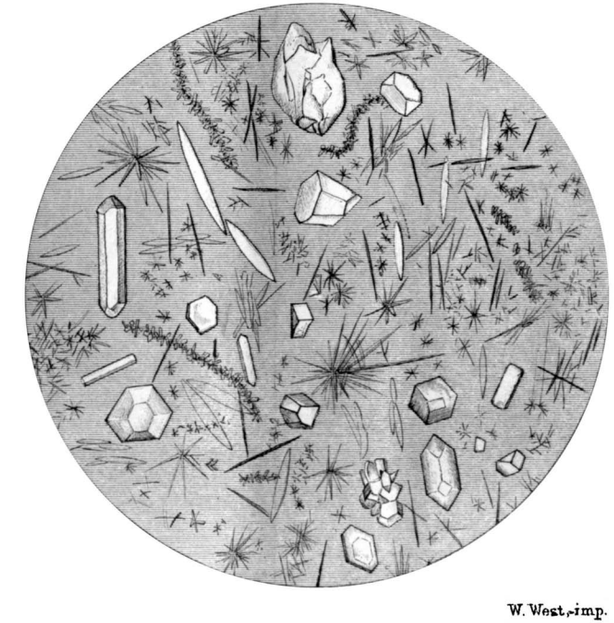


FIG: 6.



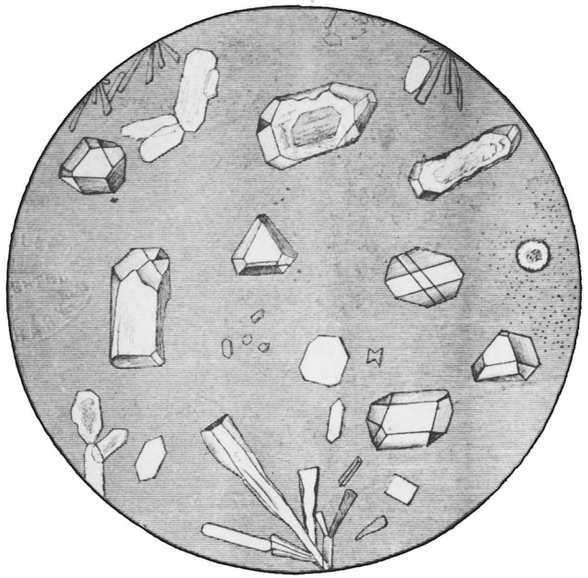
Tuffen West, sculp.

W. West, imp.

PLATE 4.

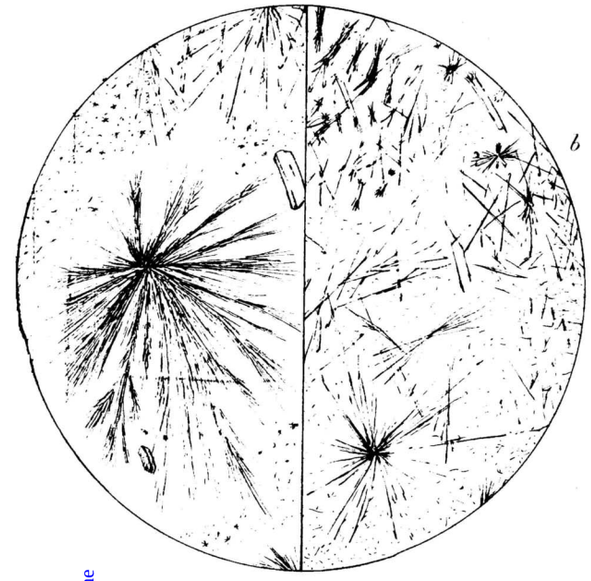
EXTRACTUM OPII.

FIG: 1.



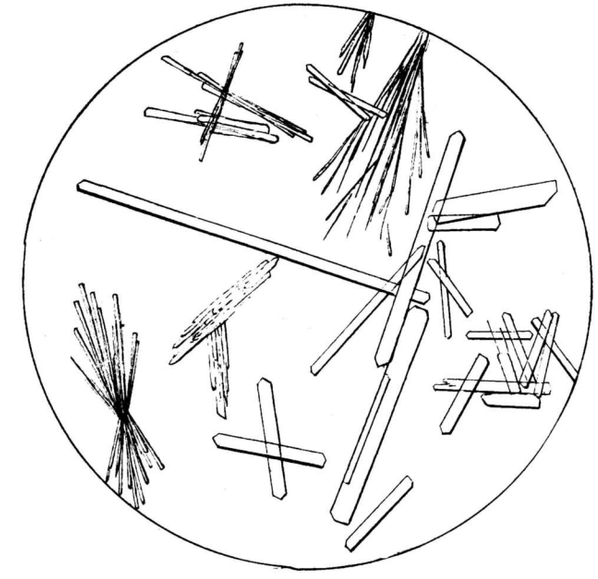
PATNA.

FIG: 2.



MALWA.

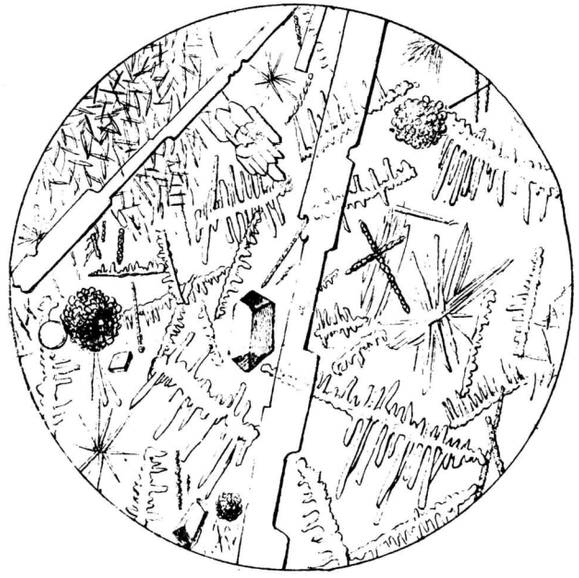
FIG: 3.



PERSIAN

TINCTURA OPII.

FIG: 4.



PATNA.

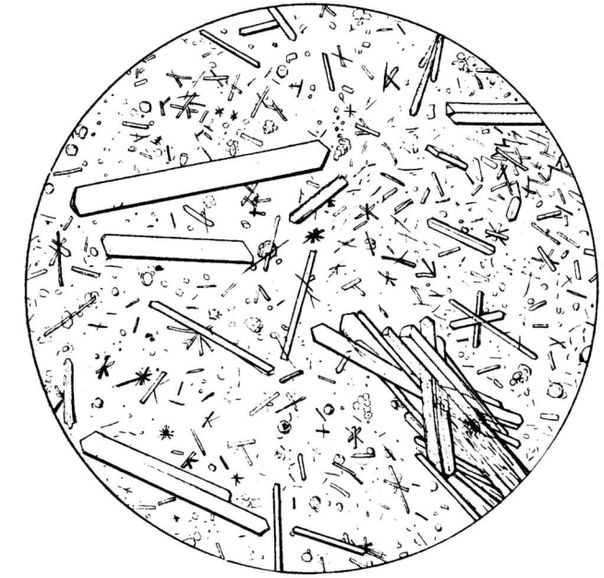
B. Brady del ad nat.

FIG: 5.

MALWA.

Tuffen West, sculp.

FIG: 6



PERSIAN.

W. West imp.

EXPLANATION OF PLATES.

PLATE I.

Microscopical Appearance of Opium Principles.

Fig. 1. Morphine.
„ 2. Narcotine.
„ 3 *a*. Sulphate of Morphine.
b. Meconate of Morphine.
ba. Commercial salt crystallized from solution in weak alcohol.
bb. Crystallization from mixed solutions of Morphia and Meconic Acid.

Fig. 4 *a*. Codeine.
aa. Crystallized from Alcoholic solution.
ab. Crystallized from Aqueous solution.
b. Thebaine.
„ 5 *a*. Meconine.
b. Meconic Acid.
„ 6 *a*. Narceine.
b. Papaverine.
ba, Crystallized from Alcoholic solution.
bb. Crystallized from Aqueous solution.

PLATE II.

Fig. 1. Tinctura Opii (Turkey Opium), prepared by the Authors as standard.
„ 2, 3. Specimens of Tincture alluded to in the text.
„ 4. Extractum Opii (Turkey).
„ 5 *a*. Commercial Extract of Opium, imported.
b. The same, redissolved, filtered, and evaporated.
„ 6. Liquor Opii Sedativus, prepared from Patna Opium.

PLATE III.

Liquor Opii Sedativus (Turkey Opium).

Fig. 1. Battley's.
„ 2 *a*, *b*. Two specimens prepared by the Authors by slightly different processes, from different samples of opium.
„ 3. Mr. Morson's alluded to in the text.
„ 4, 5, 6. Specimens sent out by three operative chemists of standing in London.

PLATE IV.

Fig. 1. Extractum Opii, prepared from Patna Opium.
„ 2. „ „ Malwa Opium.
„ 3. „ „ Persian Opium.
„ 4. Tinctura Opii, prepared from Patna Opium.
„ 5. „ „ Malwa Opium.
„ 6. „ „ Persian Opium.