Thesis

In the want of uniformity in strength of Medicinal Substances,
With an investigation of the amounts of active principle present in certain official preparations of active drugs

by

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The way to some extent look upon Medicine as holding the same relationship to the Physician as do his instruments to the Surgeon. They are the weapons by which he endeavors to combat and conquer disease, although he cannot make them to accurately carry out his desires as can the Surgeon his knife, razor, gauge and cautery. Their action will be like degree. Whilst we cannot surely hope to make Medicine, like the instruments of the Surgeon, "weapons of precision", it will be conceded that it is highly desirable that they should approach this character as
much as possible. To this end they should be presented to us of such definite and accurate strengths, that we may be fully conscious of the exact amount of remedy employed. This is especially desirable in the case of those active drugs in common use, the dose of which is small, and from the exhibition of which we look for immediate results.

This principle is at the very foundation of the Pharmacopia. In the preface to the P. B. 1847, we find the following:—

"The Pharmacopia having for its object only so much the selection as the definition of..."
substances which the physician prescribes, and which are required to be kept at one temperature and uniform strength and composition. And in the Preface of the edition of 1805 we find the following:

"Of those remedies which have already received official recognition there are many with regard to which much extended knowledge has been acquired as to their sources and scientific characters, as well as of the methods by which they may be best prepared for use in medicine. Among the objects contemplated in revising the processes for the various preparations, has been
that of promoting increased uniformity of strength and other properties especially in certain of the more active remedies.

The 'path' between the various editions of the Pharmacopoeia has always been paved with good intentions which have been duly collected and presented in the respective 'phases', but it will be generally conceded that even yet the execution in many respects falls far short of the ideal. Though many improvements have certainly been carried out in the last edition of the P. B., there are still many lamentable deficiencies. To my mind one
of there is the absence of sufficient uniformity of strength in certain of the more active remedies, and it is the main object of this investigation to demonstrate this fact. The compilers of the last edition have not been at all consistent, for which we find mixture of My Lanice (formerly impurely distilled from the bean), and ordered the impanal from an extract containing a definite ascertained amount of alkaloid, such active remedies as mixture of Acute, mixture of Opium, mixture of Oenothera, and mixture of Belladonna, are still ordered the impanal is
the old manner.
Although we find this principle of uniformity and exactness of strengths recognized in the P. B., there can be no doubt that this is not attained to such a degree as it might be, and the Physician cannot yet put such absolute reliance upon the preparations he exhibits as he should be able to.
This does not apply so much to substances of definite chemical composition, though we know that they are largely subject to accidental impurities, adulterations, and deteriorations by time. Thus we know that Besmuth...
Preparations may contain objectionable traces of arsenical ones, and that powdered Cream of Tartar may be adulterated with Alum, Bisulphate of Soda or Sulphate of Lime.

Even such a simple preparation as Lime Water, great variations may be found. I have frequently seen samples which the rough test of taste and alkalinity proved to be almost devoid of Lime, and at a recent meeting of the North British Branch of the Pharmaceutical Society a paper was read by Mr. J. Fraser on "Lime Water" in which he stated that he had found nine out of eighteen samples bought in Edinburgh below the P.B. R.
standard, are being only a tenth of the strength it ought to be. This must be due either to deterioration by time or to carbonisation in preparation, the time being allowed to become converted into carbonate. Great want of uniformity may be expected in medicines derived from vegetable and animal sources. Pèreira says, "Most of the medicines prepared from animal and vegetable substances are mixtures in indefinite proportions of ingredients the chemical nature of which cannot be defined with accuracy." When we add to these natural variations those which may be due to different methods and care in the collection and preparation.*

* "Elements of Native Medicine," p. 2
of the crude drugs, to determinations by time and heat preservation, to accidental or intentional adulterations, and to different degrees of Caution in the manufacture of preparations from these drugs, it may be assumed that there is room for considerable diversities in the products which reach the physicians' hands.

Opiate may be taken as an example of a drug which shows great differences in the amounts of active principles contained in different specimens even of the same commercial variety. Thus Merck examined five specimens of morphine Opiate, free from adulteration, and
obtained quantities of Morphine varying from 3 to 4 per cent to 13 per cent. Some specimens of Constantinople Opium have yielded only 3 per cent of Morphine. In other, 44 to 15 per cent has been found.

Again, owing to different methods and care in preparation, and to numerous adulterations, Opium is brought into the market of very unequal degrees of purity, while its consistency varies greatly.

Large quantity of water being present in some specimens. According to W. T. Thornton, one fourth part of ordinary Turkish Opium generally consists of impurities, such as sand,
ashes, seeds of different plants, extracts of the Poppy from Arabic,tragacanth, aloes, small stones, minute pieces of lead and iron. Peruvia obtained 600 grains of small stones and grano from 10 ounces of opium, in proportion of about one-seventh. In England a sophisticated opium was once put in the market and largely sold, from which the morphine must have been extracted by some process as it was found to be quite devoid of that alkaloid.

These are only some of the adulterations to which opium has been subjected. Although methods are prescribed for the assay of—

Opium, there can be no doubt that in the ordinary retail trade the quality is boldly judged by the naked eye appearance. There have been proposed in France to adopt some standard, and by mixing panels of different strengths in proper proportions to get an opium which should always be the same. In a paper on "Opium," D. Squibb has treated this subject and proposes a preparation which whatever may be the strength of the opium used should always have a fixed value. Such a preparation should not be difficult to devise or prepare, and certainly would be of much practical value.

* "American Journal of Pharmacy" March 1860 p. 115
The leaves and roots of plants vary in activity according to the time of year at which they are collected, and although those which are official are ordered to be collected at special seasons, we have no sufficient guarantee that they are so. Thus Persius says that Digitalis leaves of the fifth year growth are often substituted for those of the second year, to which they are much inferior in activity, and that Hyoscyamus leaves to be found in most drug shops are comparatively worthless being derived from the biennial plant which is much inferior in activity to the biennial which alone is official.
In the British Medical Journal of Feb.
27th 1846 there is a notice giving the
results of an enquiry carried out by
Dr. Edward Seaton, and Mr. Otto
Reynor in the Port of Chile.
Fifty prescriptions were sent out to
various ships, and allowing a
liberal margin for errors, none of
the prescriptions were scheduled
as incorrectly made up if the
chief constituent was within 10
per cent of the amount ordered.
No fewer than seventeen out of
the fifty were incorrectly dispensed
and the limits of error were very
wide indeed, for in one case the
quantity of the drug supplied was
less by 85 per cent than that
ordered, and in another 57 per
cent more than had been ordered.

One can scarcely credit that such wide divergencies could be due to mere inaccuracy in weighing or measuring, or personal carelessness in dispensing. It is now probable that it was largely due to variations in drugs or preparations arising from some of the causes which I have indicated.

In following out this subject I have been led to investigate the amount of active principle present in each different specimen of certain official preparations of active drugs, and the variations which I have found have been so striking as to make me consider...
the results of the investigation worthy of being recorded.

The substances investigated were Tincture of Aconite, Tincture of Opium, Tincture of Digitalis, Extract of Meshonica, and Extract of Belladonna. Four specimens of each were obtained from widely different sources, and the amount of active principle present in an equal quantity of each of the four specimens was estimated, the same process being followed in each case, under similar circumstances and with as much care as possible.

1. Tincture of Aconite. The four specimens varied somewhat in colour, this being of different shades.
of Sherry Colour, due to dark as to be of a medium Port Wine Colour.
One pint was the quantity subjected to examination in each case. This
was evaporated over a water bath,
and the residual extract was
mixed with twice its weight of
boiling distilled water, and after
cooling, filtered through paper.
Solution of uronema was now
added in slight excess, and the
liquid treated gently over a
water bath. The precipitate of
impure Acetone was then separated
on a filter, dried, and macerated
in successive portions of pure
Ether. The general products were
mixed and the Ether evaporated,
the dry extract being then dissolved
in warm distilled water acidulated with dilute sulphuric acid. The acetate was precipitated from this solution when cold by the cautious addition of solution of ammonia dilute with distilled water. The precipitate was then collected on a filter and dried.

In this process the impure acetate precipitated from its combination with acetate acid by the solution of ammonia is purified by digesting in ether in which the impurities are insoluble, and after solution in the acidulated water is again precipitated by ammonia.

Of the four specimens No. 1 (the darkest) yielded 4.5 francs, No. 2, 5 francs, No. 3, 8 francs, No. 4, 8 francs.
Prof. Van Porter obtained 0.85 percent from the root cultivated in America, which would be equal to about 9 grains from the root of opium of Fortune. He found the unfermented root considerably poorer in alkaloids.

2. Tincture of Opium. Six ounces and one drachm (fluid) equivalent to 200 grains of opium, was evaporated over a water bath. The residual extract was dissolved in eight ounces distilled water and boiled with 200 grains of plaster lime for 10 minutes. This was placed on a filter and the unevaporated matter washed with two ounces boiling water. The filtered fluid was acidulated slightly with dilute hydrochloric acid, evaporated.
to the bulk of 1 ounce and let Cool. The liquid was then neutralised with solution of Ammonia, an excess being avoided, and the brown matter separated removed by filtration, washed with hot water, the washings being added to the filtrate. The liquid was then Concentrated to one ounce and Solution of Ammonia added in slight excess. After standing 24 hours, the precipitate of Morphine was collected on a filter and dried. In this process the base combines with the Phenolic acid and Sulphuric Acid with which the Morphine is Combined in the Grain. The Morphine is subsequently precipitated by the addition of Solution of Ammonia in slight excess.
No 1, 16 grms., No 2, 14 grms.
No 3, 19 grms., No 4, 20 grms.,
equal to 4.5, 7, 9.5 and 10 per cent of
Morphine.

3. Mixture of Digitalis:
One part of the mixture was
Evaporated over a water bath and
the residual extract mixed with
half an ounce distilled water to
which half a dram of nitric
acid had been added. The solution
thus formed was diluted with
10 grains of sodium carbonate,
then filtered, and the filtrate
Diluted with distilled water
until it measured 1/2 ounces.
Solution of ammonia was now
added nearly to neutralisation,
and afterwards 10 grains of sodium.
Acid dissolved in 2 drachms of water. The precipitate formed was then washed with a little distilled water, mixed with a small quantity Rectified Spirit and 10 grains Oxide of Lead. The mixture was then put in a small flask with a little Rectified Spirit and kept at a temperature of 160° for about an hour. 10 grains of Sperm phosphoric Acid Charcoal was then added, the mixture put on a filter, and the Spirit carefully driven off from the filtrate by the gentle heat of a water bath.

In this process, the Digitalis is taken up by the Acetic Acid, the extractive and resinous matters being left undissolved. After partial decolorisation
the solution is nearly neutralised by ammonia, and the Digitalis precipitated by the I ammo acid. It is then rubbed up with oxide of lead which combines with the I ammo acid forming insoluble I ammoate of lead. The Digitalis is next dissolved in spirit, the solution decoloured, filtered, and the spirit distilled off at a gentle heat.

No 1 yielded 9 grains, No 2, 9 grains
No 3, 12 grains, No 4, 14 grains.

4. Extract of New I amine.
The four specimens were obtained from different manufacturers in London. Their solutions in water when filtered presented very marked differences in colour, from pale chesty to a full Port Wine colour.
Half an ounce of the extract was rubbed up with 3 1/2 ounces warm distilled water, and the solution filtered when cold. A solution of 45 grains of acetate of lead in a little distilled water was then added so long as it occasioned any precipitate. The fluid was then filtered, the precipitate washed with 2 1/2 ounces cold distilled water, and the washings added to the filtrate and the clear fluid evaporated to 2 ounces. When it had cooled solution of ammonium was added in slight excess, stirring thoroughly, and the mixture allowed to stand for twelve hours. The precipitate was then collected on a filter, washed with a little cold
distilled water, and dried over a water bath.

In this process, the acetate of lead forms acetates of strychnine and
brucine and precipitates the Iasmin acid with which they are combined
in the seeds, together with Resin to which are separated by filtration.
After evaporating the filtrate, Ammonia is added in slight excess to
precipitate the alkaloids.

No. 1 yielded 22 grams, No. 2, 24 grams,
No. 3, 28 grams, No. 4, 32 grams.

This result is the more interesting as it shows that only one of
the specimens contained the
15 per cent of total alkaloid
ordered to be contained in the latest edition of the Pharmacopæia.
5. Extract of Pelladona

Half ounce of the extract was rubbed up with 10 ounces warm distilled water, and after cooling shaken with half an ounce boiled lime several times. The mixture was filtered, diluted sulphuric acid added in very small excess to the filtrate, which was then filtered again. The fluid was then evaporated at a gentle heat to about 2 ounces and after cooling a solution of Carbonate of Potash carefully added with constant stirring, so as nearly to neutralize the acid. After having stood for half an hour the fluid was filtered and Carbonate of Potash added in solution till the liquid acquired a decided alkaline.
A reaction. It was then shaken briskly in a bottle with 1/2 ounces Chloroform, and after the Chloroform had subsided it was drawn off and evaporated gently over a water bath, and the residual fine pure Atropaia weighed. Belladonna contains Atropaia in the form of Bi-Malate. This salt is decomposed by the Zinc which removes the Hydrochloric acid and colouring substance matter. Dilute Sulphuric acid is added to unite with the Atropaia, as the alkaloid is easily decomposed by heat. A small quantity of Carbonate of Potash is added to separate a viscous substance, and then an excess of Solution of Carbonate of
Potash is added to precipitate the
Astatine which is removed from the
mixture by solution in the Chloroform.
No. 1 yielded 4 grains, No. 2, 4.5 grains,
No. 3, 3 grains, No. 4, 3 grains.

In concluding this article, I would
submit that the marked difference
in strength of these preparations
disclosed by this investigation
renders them unsatisfactory, and
that it is highly desirable that
should possess a greater
uniformity. In the case of mixture
of Astatite, which preparations shewed
the greatest want of uniformity,
I am aware that two of the
specimens were prepared from
bags in this season's Collection.
the others presumably from root
which had been lying in stock
some time.
The whole question of rendering
the medicines more reliable of more
certain and uniform strength is
one which is entitled to serious
consideration. With a view to
its solution I would make the
following suggestions, which if
adopted would I think give
to the Physician much greater
confidence in using remedies,
and probably more success
and satisfaction in dealing
with disease.
1st. I would have a large permanent
Pharmacopoeial Committee which
should embrace some of the leading
Pharmacists, Chemists, and
Superintendents of the Kingdom, and
whose duties should be continuous
and not spasmodic. It should
be the duty of this Committee to
investigate thoroughly and collect
information regarding all new remedies,
and to stamp with their approval
such as they consider useful
additions to the Materia Medica.
It should also be their duty to
investigate thoroughly the drugs
and preparations in use, especially
the more active ones, and to
endeavour to obtain some standard
preparations, such as Extracts,
Containing definite and uniform
proportions of active principles.
The results of their labours should
be embodied in editions of the Pharmacopoeia or in additions which should appear at not longer intervals than five years. 2. The should exercise a close interest than many doctors in the dispensing of our prescriptions, seeing that they are made up if possible by local houses such as will be likely to keep their drugs and chemicals most fresh and pure. To this end we should discourage doctors shops, though in many country districts there are from the circumstances incumbrance evils, for medical man as a rule have within the time nor the capability for judging of the quality and
testing the purity of drugs. We should also educate the public to avoid all such stores as Cooperative and Cheap drug stores, and to recognize in the Pharmacy not an ordinary tradesman but a scientific worker for whose knowledge, experience and care they should be ready to pay with no grudging heart.

In the investigation previously referred to as Carried out by Mr. Seaton and Chulsoh Tombs found that 75 per cent of the prescriptions dispensed by "drug companies" were untrustworthy, that 50 per cent of those from doctors belonged to the same category.
included 20 per cent of those dispensed at Cooperative stores also exceeded the margin of error. The moral is obvious when we learn that only 20 per cent of those dispensed at a regular druggists exceeded the margin of error.

3rd. I would have in each large centre of population an inspector of drugs, paid either by Government or from local taxation. This inspector should have the supervision of a certain district, and it should be his duty to examine and analyze drugs and chemicals offered for sale or used in dispensing. This present provision of carriers carried out
under the Food and Drugs Act, is utterly inadequate to the importance of the matter. In practice, it is a mere farce, at least so far as drugs are concerned. I hope to carry on this investigation further, to verify the results obtained, and to examine other articles of the Materia Medica. I think the labour will be well spent, for the subject seems to me one of considerable importance. In dealing with such potent remedies as are now in common use, it is purely of some importance to have them in such forms that we can put through reliance in their being of
uniform strength and purity.

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