

Thesis

On 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
Richard B. Macpherson
M.B. Ch.

ProQuest Number:27552861

All rights reserved

INFORMATION TO ALL USERS

The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if material had to be removed, a note will indicate the deletion.



ProQuest 27552861

Published by ProQuest LLC (2019). Copyright of the Dissertation is held by the Author.

All rights reserved.

This work is protected against unauthorized copying under Title 17, United States Code
Microform Edition © ProQuest LLC.

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

1
We may to some extent look upon Medicines as holding the same relationship to the Physician as do his instruments to the Surgeon. They are the weapons by which he endeavours to combat and conquer disease, although he cannot make them so accurately carry out his desires as can the Surgeon his Knife, nor gauge and control their action in a like degree.

Whilst we can scarcely hope to make Medicines, like the instruments of the Surgeon, "weapons of precision", it will be conceded that it is highly desirable they should approach this character as

much as possible. To this end they should be presented to us of such definite and accurate strength, 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 Pharmacopœia.

In the preface to the P. B. 1847, we find the following —

"The Pharmacopœia having for its object not so much the selection as the definition of

substances which the Physician prescribes, and which are required to be kept at one safe and uniform standard of strength and composition".

and in the preface to the edition of 1885 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 Pharmacopœia has always been paved with good intentions which have been duly collected and presented in the respective prefaces, 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. In my mind one

of these 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 whilst we find Tincture of
 Nux. Vomica, (formerly prepared
 directly from the bean), now
 ordered to be prepared from an
 extract containing a definite
 ascertained amount of alkaloid,
 such active remedies as Tincture
 of Acacia, Tincture of Opium,
 Tincture of Hyptis, and
 Tincture of Belladonna, are
 still ordered to be prepared in

the old manner.

Although we find this principle of uniformity and exactness of strength recognized in the P. B., there can be no doubt that this is not attained to such a degree as it ought be, and the Physician cannot yet put such absolute reliance upon the preparations he exhibits as he should be able to.

Substances 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 Bismuth

Preparations may contain objectionable traces of arsenical ones, and that powdered Cream of Tartar may be adulterated with Alum, Bisulphate of Potash or Sulphate of Lime.

iv

Even ~~with~~ such a simple preparation as Lime Water, great variations may be found. I have frequently seen samples which the rough tests of taste and alkalinity showed 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. 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.

standard, one being only a tenth of the strength it ought to be. This must be due either to deterioration by time or to carelessness in preservation, the Linc being allowed to become converted into Carbonate. greater want of uniformity may be expected in Medicines derived from Vegetable and Animal sources Pereira 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.

of the crude drugs, to deteriorations by time and bad preservation, to accidental or intentional adulterations, and to different degrees of carelessness in the manufacture of preparations from these drugs, it may be surmised that there is room for considerable diversities in the products which reach the Physicians hands.

Opium may be taken as an example of a drug which shows great differences in the amounts of active principle ~~obtain~~ contained in different specimens even of the same Commercial variety.

Thus Merck examined five specimens of Smyrna Opium, free from adulteration, and

obtained quantities of Morphia varying from 3 or 4 per cent to 13 per cent. Some specimens of Constantinople Opium have yielded only 3 per cent of Morphia, in others 14 or 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 consistence varies greatly a large quantity of water being present in some specimens.

According to W. A. J. Thomson, one fourth part of ordinary Turkey Opium generally consists of impurities, such as sand,

ashes, seeds of different plants, extracts of the Poppy, Gum Arabic, Tragacanth, Alas, small stones, minute pieces of Lead and Iron. Pereira obtained 600 grains of small stones and gravel from 10 ounces of Opium, a proportion of about one-seventh. In England a sophisticated Opium was once put in the market and largely sold from which the Morphin 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 assaying of

* U.S. Dispensatory, 13th Edition, P. 631

Opium, there can be no doubt that in the ordinary retail trade the quality is solely judged off by the naked eye appearance.

It has been proposed in France to adopt some standard, and by mixing parcels of different strengths in proper proportions to get an opium which should always be the same. In a paper on "Opium", * Dr. 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 Pereira says that *Digitalis* leaves of the first year growth are often substituted for those of the second year, to which they are much inferior in activity, and the *Hyoscyamus* leaves to be found in most drug shops are comparatively worthless being derived from the annual plant which is much inferior in activity to the biennial which alone is official.

In the British Medical Journal of Feb^{ry}
27th 1886 there is a note giving the
results of an enquiry carried out by
Dr. Edward Leaton, and Mr. Otto
Keyser in the Parish of Chelsea.

Fifty prescriptions were sent out to
various shops, 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 general carelessness in dispensing. It is now probable that the error 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 specimens 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 *Mor. Romica*, 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, thus being of different shades

of Shiny Column, one so 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 Ammonia was now added in slight excess, and the liquid heated gently over a water bath. The precipitate of impure acetica was then separated on a filter, dried, and macerated in successive portions of pure Ether. The several products were mixed and the Ether evaporated, the dry extract being then dissolved

in warm distilled water acidulated with diluted Sulphuric acid. The Acetic acid was precipitated from this solution when cold by the cautious addition of Solution of Ammonia diluted with distilled water. The precipitate was then collected on a filter and dried.

In this process the impure Acetic acid precipitated from its combination with Acetic 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 grains, No 2, 5 grains, No 3, 8 grains, No 4, 8 grains.

Prof. Wm Procter obtained 0.85 per cent from the root cultivated in America, which would be equal to about 9 grains from one pint tincture of Acornite. He found the imported root considerably poorer in alkaloid.

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 slaked lime for 10 minutes. This was placed on a filter and the undissolved 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 neutralized 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 Lime combines with the Meconic acid and Sulphuric acid with which the Morphine is combined in the Opium. The Morphine is subsequently precipitated by the addition of solution of Ammonia in slight excess.

No 1 Guldbeck 13 grains, No 2, 14 grains
 No 3, 19 grains, No 4, 20 grains,
 equal to 6.5, 7, 9.5 and 10 percent of
 Morphine.

3. Tincture of Digitalis

One pint of the Tincture was
 evaporated over a water bath and
 the residual extract mixed with
 half an ounce distilled water to
 which half a drachm of Acetic
 Acid had been added. The solution
 thus formed was digested with
 10 grains Purified Animal Charcoal,
 then filtered and the filtrate
 diluted with distilled water
 until it measured $1\frac{1}{2}$ ounces.
 Solution of Ammonia was now
 added nearly to neutralization,
 and afterwards 10 grains of Laune

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 purified Animal 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 Digitalin 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 Digitalin precipitated by the Tannic Acid. This then rubbed up with oxide of lead which combines with the Tannic acid forming insoluble Tannate of lead. The Digitalin is next dissolved in Spirit, the solution decolorised, filtered and the Spirit distilled off at a gentle heat.

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

4. Extracts of Nux Vomica.

The four specimens were obtained from different manufacturers in London. Their solutions in water when filtered presented very marked differences in colour, from pale cherry to a full Port Wine colour.

Half an ounce of the extract was rubbed up with $3\frac{1}{2}$ 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 $2\frac{1}{2}$ 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 Ammonia 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 Strychnia and Brucea and precipitates the Igasuric Acid with which they are combined in the seeds, together with Resin &c which are separated by filtration. After evaporating the filtrate, Ammonia is added in slight excess to precipitate the alkaloids.

No 1 Gilded 22 grains, No 2, 24 grains,
No 3, 28 grains, No 4, 32 grains

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 extract of the last edition of the Pharmacopœia.

5. Extract of Belladonna

One ^{half} ounce of the extract was rubbed up with 10 ounces warm distilled water; and after cooling shaken with half an ounce slaked Lime several times. The mixture was filtered, diluted Sulphuric Acid added in very feeble 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 neutralise the acid. After having stood for six hours the fluid was filtered and Carbonate of Potash added in solution till the liquid acquired a decided alkaline

reaction. It was then shaken briskly in a bottle with $1\frac{1}{2}$ ounces Chloroform, and after the Chloroform had subsided it was drawn off and evaporated gently over a water bath, and the residual impure Atropia weighed.

Belladonna contains Atropia in the form of Bi-Malate. This salt is decomposed by the Lime which removes the organic acid and colouring extractive matter.

Dilute Sulphuric Acid is added to unite with the Atropia, as the alkaloid is easily decomposed by heat. A small quantity of Carbonate of Potash is added to separate a resinous substance, and then an excess of Solution of Carbonate of

Potash is added to precipitate the Atropine 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 differences in strength of these preparations disclosed by this investigation render them unsatisfactory, and that it is highly desirable they should possess a greater uniformity. In the case of mixture of Acute, which preparation showed the greatest want of uniformity, I am aware that two of the specimens were prepared from roots of this seasons Collection.

the others presumably from root
which had been lying in stock
some time.

The whole question of rendering
the Medicines we exhibit 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
accepted 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
 Therapeutists 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.

2nd - We should exercise a closer interest than many of us do in the dispensing of our prescriptions, seeing that they are made up if possible by good houses such as will be likely to keep their drugs and chemicals most fresh and pure.

✓
or
dispensing
by
Doctors

To this end we should discourage doctors shops, though in many country districts there are from the circumstances necessary evils, for medical men as a rule have neither 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 snare as Co-operative and Cheap drug stores, and to recognise in the Pharmacist not an ordinary tradesman but a scientific worker for whose knowledge, experience and care they should be ready to pay with no grudging hand.

In the investigation previously referred to as carried out by Dr. Seaton at Chelsea it was found that 75 per cent of the prescriptions dispensed by "drug companies" were untrustworthy, that 50 per cent of those from doctors shops belonged to the same category.

which 20 per cent of those dispensed at cooperative stores also exceeded the margin of error. The moral is obvious when we learn that only 6 per cent of those dispensed at a regular druggists exceeded the margin of error.

3rd I would have in each large center 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. The present provision as ~~carried~~ carried out

under the Food and Drugs act
is utterly inadequate to the
importance of the matter. In practice
this is a mere farce, at least as
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 surely of some importance
to have them in such forms
that we can put thorough
reliance on their being of

uniform strength and purity.

R B Macpherson
M.D.