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OUTLINE OF MICRO-ANALYTICAL METHODS FOR FOOD AND DRUGS LABORATORIES.*

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The value of the compound microscope as a ready means for determining the identity, quality and purity of foods and drugs is, thus far, underestimated. It is true that the work of the micro-analyst as an adjunct to the work of the chemist receives certain recognition. It is however also true that the micro-analysts form a very decided minority, as there are today perhaps not more than a dozen actively employed micro-analysts in the United States. These have thus far had no meetings at which methods might be discussed and formulated, neither have they organized for such purposes.

The old-time microscopical societies have practically passed out of existence. These societies performed an excellent service in developing methods of technique, and did much toward developing and perfecting the mechanism of the compound microscope, but the work along the lines of biological study among the members did not keep pace with the purely mechanical technique, and their efforts became more and more amateurish, in the comparative sense, and finally the interest in the "Marvels revealed through the microscope" passed, and with it the society. Those microscopists having knowledge of biology, entered the field as specialists in bacteriology, pathology, botany and anatomy, limiting themselves to a comparatively narrow field of work. The micro-analyst, in the broader sense, is a very recent product.

Without further preliminaries, I shall briefly outline what suggests itself as a better adjustment of the work done by analytical chemists, micro-analysts and bacteriologists.

The analytical methods, as they apply to the critical examination of foods and drugs, as to purity and quality, are chemical, microscopical and bacteriological. The substances to be analyzed may be grouped as follows:

1. Vegetable drugs, crude and powdered, pharmacopoeial and other medicinal compound powders.
2. Spices and condiments, whole, ground and powdered, prepared spices and condiments.
3. Coffee, tea, cocoa, chocolate, confections, candies.
4. Tobacco and preparations made from tobacco, as snuff, smoking tobacco, cigars, etc.
5. Chemicals, minerals, solutions of chemicals, etc.

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6. Tablets, pills, powders.
7. Meats of all kinds, raw, cooked, canned, sausage meats, etc.
8. Dairying products, as milk, cream, cheese, butter, cream fillers, including ice cream, etc.
9. Insect powders, dusting powders, cosmetics.
10. Cattle and poultry powders.
11. Unknown powders, wholly or partly of vegetable origin.
12. Starches, dextrins, sausage meat binders (starches).
13. Vegetable foods, as jams and jellies; fresh, pickled, cooked, canned and preserved.
14. Flours and meals.
15. Breakfast foods, infant and invalid foods.
16. Breads and similar materials; biscuits, doughnuts, cakes, pies, pastries, etc.
17. Macaroni, spaghetti and similar preparations, noodles, etc.
18. Nuts and nut-like fruits and seeds, etc.
19. Beverages of all kinds, liquids generally.
20. Pharmaceuticals of all kinds.
21. Patent and proprietary medicines.
22. Unknown foods and medicines.

In the examination of some of these substances the chemical method is all-important, as in chemicals generally; in others the microscopical method is all-important, as in meals, flours, spices; and again the bacteriological testing is all-important, as in sewage, contaminated water, contaminated milk, infected foods and drinks generally, etc. A properly equipped analytical laboratory, whether federal, state or private, should be prepared to apply all three methods. The bacteriological investigations should be made by the micro-analyst rather than by the chemist, because of the closer relationship between bacteriology and microscopy.

Just what work should or should not be done by the micro-analyst is as yet not definitely determined; at least, there is no uniformity as to scope of action in the different analytical laboratories. Based upon experience and observation, it is suggested that the following work be assigned to the micro-analyst:

1. Gross and net weight determination of all such samples as require it.
2. Moisture determination of substances which require it.
3. Ash and acid insoluble determinations of substances which are primarily subject to microscopical analysis, as vegetable drugs, pills, powders, vegetable compound powders, etc.
4. Use of certain special tests, as sublimation tests for benzoic acid, salicylic acid and boric acid; Grahe's cinchona test, wheat gluten test, color reactions for boric acid, capsicum, guaiac, salicylic acid, morphine, etc., tests for cholesterol and phytosteral crystals, and others which may prove useful.
5. Bacteriological testing of sera, vaccines, galenicals, syrups, milk, water, jams, jellies, catsups, etc., as may be required, following the method of the Society of the American Bacteriologists, and limiting the testing to determining the presence or absence of the colon bacillus and other sewage organisms, and the usual quantitative bacterial determinations for milk, water and other substances, of which the quality is usually based upon the quantitative bacterial content.

Substances subject to analysis in the laboratories mentioned should be grouped or classified according to the special or preferred methods of examination to be applied. It is, of course, evident that in the majority of cases chemical as well as microscopical methods should be applied. In some cases even all three must be

used in order that conclusive results may be obtained. The following grouping is suggested:

1. Substances in which the chemical analysis is of first importance. Chemicals generally, and chemicals in solution, alcohol, alcoholic drinks, flavoring extracts, syrups, oils, fats, etc.

2. Substances in which the microscopical analysis is of first importance—vegetable substances and preparations which are essentially of vegetable origin. Meats of all kinds, variously prepared, cooked, spiced, etc.

3. Substances in which the chemical and microscopical examinations are of equal importance—assayable vegetable drugs, all prepared food substances with chemicals in solution, compound powders, pills, tablets.

4. Substances to which the microscopical examination is not generally applied—chemicals, liquids in which the insoluble particles are slight in amount, as wines, brandies, beers, comparatively pure solutions, etc. Here the centrifuge plays an important part.

5. Substances in which the bacterial testing is of prime importance—milk, sewage or otherwise organically contaminated water supplies, and other liquids, beers, etc., contaminated foods generally. In this class of substances the microscopical and chemical examinations become necessary in addition to the bacteriological; in fact, a bacteriological test is incomplete without the use of a good compound microscope.

The work of the micro-analyst is, so to speak, on trial. The doubt in the minds of the critics is due, very largely, to the unsatisfactory results traceable to the efforts of those who are not sufficiently qualified. Even the most skillful analysts admit numerous defects and shortcomings in methods and in results. For example, the quantitative estimates based upon optical judgment are approximate only, and with most workers there is a very marked tendency to make these estimates volumetric rather than gravimetric. This can in a measure be corrected by bringing into play the judgment of the relative weights of the several substances under comparison. For example, the amount of sand present in powdered belladonna root may be volumetrically estimated at 20 per cent. In this case the acid insoluble ash residue may show 35 to 40 per cent. of silica. An example like this also indicates why the micro-analyst should make the sand and ash determinations. The percentage estimates based upon microscopical examination may vary within 25 to 50 per cent. when small amounts of admixtures are considered. For example, the actual amount of arrow-root starch in the so-called arrowroot biscuit is, I believe, 2.5 per cent. The micro-analyst's estimates may range from a trace or small amount to 5 per cent. When the quantities of admixtures are large, from 30 to 90 per cent., the estimations may approximate within 10 or 15 per cent. of the actual amount present. These estimates can no doubt be made much more accurate by uniform methods of technique, aided by certain mechanical devices. For example, in the examination of vegetable powders, spices, meals, flours and similar substances, the samples should be thoroughly mixed, and slide mounts should be of standard and uniform thickness and the relative amounts of the ingredients should be estimated by means of microscope slides having uniform ruled squares of definite measuring value in microns. These and other details in the methods should be more fully worked out.

Several micro-analysts have declared themselves as opposed to giving percentage estimates of the several ingredients of a compound. However, not to give the approximate percentages will cause great confusion and very materially lessen the value of the work done. For example, to report a pancake flour as

composed of "buckwheat and wheat flour, the former predominating," instead of "buckwheat 75 per cent. and wheat 25 per cent.," would certainly be unsatisfactory.

The following examples will serve to explain the relative value of the chemical and microscopical analyses. Suppose the substance to be examined is a baby food. The microscope may reveal approximate percentages of oil globules, steam dextrinized wheat starch, unchanged wheat and arrowroot starch, wheat tissue and milk sugar. The chemical analysis will show a definite percentage of sugar, soluble starch, insoluble starch, fat, vegetable fiber and ash. This is a good example of a case where the two methods of analysis are of equal importance; one without the other would be unsatisfactory, incomplete and inconclusive. Again, the chemical assay may show that a sample of powdered or crude belladonna leaf contains 0.35 per cent. of mydriatic alkaloids, and yet the microscopical examinations may prove the presence of 30 per cent. or more of some foreign leaf.

An adjunct in analytical work, much neglected by the chemist, is the organoleptic testing. This is especially important in the examination of unknown substances, fruit products, spices, meats, etc., as it often gives a clue to the quality of the substances and to the means of getting quick results.

The equipment and apparatus required by the micro-analyst is comparatively inexpensive, yet it is very earnestly advised to secure only those appliances which are useful or essential for the work in hand. The following list is submitted without entering into detail, as it may be assumed that the microscopist does not require detailed explanations:

1. Simple lens.
2. Compound microscope.
   a. Ocular with micrometer scale.
   b. Oculars, Nos. 2 and 4.
   c. Objectives, Nos. 3, 5 and 7.
   d. 1/12 in. oil-immersion objective for bacteriological work.
3. Slides and covers.
4. Section knife or razor, and strop.
5. Polarizer, for the study of starches, crystals and other substances. Should be convenient to use. The selenite plates are useful.
6. Thoma-Zeiss hemacytometer; for counting yeast cells and bacteria.
7. Stage mould and spore counter, as described in this paper (Figs. 1 and 2).
8. Accurate metal or hard rubber millimeter ruler for measuring seeds (in fruit products), etc.
9. The required glassware and adjunct apparatus.
10. The required reagents.
11. Equipment for making moisture determinations.
12. Equipment for making ash determinations.
13. Equipment for the required bacteriological determinations.

The laboratory in which the work is done must be roomy, well-lighted, provided with the necessary shelves, apparatus and supply cases, reference books, etc. The details cannot be given here. The analyst must see to it that the necessary things are provided. A skillful worker should have the tools of his choice, not those selected for him by some one not qualified to judge.

It is wholly impracticable to enter into a full discussion of the technique and methods to be employed by the micro-analyst. The following are mere suggestions which, it is hoped, may serve as a guide to a unification of methods. There are many other matters of detail which cannot be discussed in a brief report, such as the preparation of standard micro-chemical reagents, use of new reagents and the discontinuance of reagents which were at one time considered of great value but which later experiences have proven to be unessential, etc.

A uniform tissue terminology is of great importance in comparing results in the critical examination of vegetable foods and drugs. The terms used should be uniformly interpreted and applied by all analysts. This does not appear to be the case, as will become evident from a comparison of the terms used by the several authors on botany and pharmacognosy. The following is a convenient classification of tissues, giving examples for purposes of ready demonstration.

Trichomes or hair cells.

Simple: Single-celled, walls thick or thin, smooth or rough, warty, etc.; as in tea, sage, apricot, peach, strawberry, raspberry, loganberry, etc.

Many-celled, as in digitalis, hyoscyamus, belladonna, etc. Cell-walls may be smooth or rough, warty, etc.

Aggregate or stellate; as in mallows, castanea, hamamelis, etc.

Branching; as in mullein.

Glandular; as in the mints, tobacco, nettle. Kamala and lupulin, are usually designated glands.

Emergencies; rather rare and of no special diagnostic value. Pappus, chaff, etc.

Unusual trichomatic structures; T-shaped as in chrysanthemum, shield-shaped as in the olive leaf, etc.

Epidermis. In plants, a single layer of cells including the trichomes above mentioned. The cells differ greatly as to thickness and form of cell-walls, as to cell-contents, etc.

Cuticle: The outer or external wall, with various projections and markings. Variable in thickness.

Vertical cell-walls: These may be wavy or straight, warty, porous, etc.

Stomata: Somewhat variable as to size but the structural variations are not sufficiently marked to be of any special diagnostic value. Their occurrence and distribution on upper and lower surfaces of leaves may be diagnostic.

Nebenzellen (neighboring cells): May be of great diagnostic value, dependent upon arrangement, number, size and form of cells and character of cell-contents.

Collenchyma. Angles of cell-walls thickened.

Parenchymatous: Cells nearly isodiametric or slightly elongated, as in gentian.

Bast-like. Cells much elongated, the usual form, as in labiate stems. (Characteristic thickenings of the angles of cells seen in transverse section.)

Palisade cells or tissue. Elongated cells usually placed vertically to surface, as the palisade tissue of the leaves, of the seed-coat (or testa) of many seeds (bean, pea, mustard, apple and quince seed, etc.)

Bast cells or bast fibers. Cell-walls with or without lignin, comparatively non-porous. Ends tapering pointed.

Typical: Greatly elongated cells, extremely flexible, colorless, usually non-lignified. Typically developed in willow bark, in cotton-root bark, mezereum, etc.

Sclerenchymatous: Short cells with greatly thickened usually porous lignified walls. Typically developed in the cinchona barks, cinnamon barks, sassafras bark, etc.

Branching: Cells more or less branching at the ends, as in wild-cherry bark, soap bark, etc.

Sclerenchyma or stone cells. Usually greatly thickened, porous walls, which are universally lignified. Many are of a brownish color.

Typical: Approximately isodiametric, may be thick walled, thin walled or with walls unevenly thickened. Widely distributed in the plant kingdom; found in nut shells, in fruits, in barks, in roots, etc.

Elongated or bast-like: Differ from bast cells in that the ends are truncate instead of tapering pointed.

Branching: As in tea leaves, in some nut shells, seed pits, etc.

Wood fibers or wood cells. Differ from bast in that the fibers are more firmly bound together, always lignified, more porous, and ends usually very blunt, or truncate and diagonally cut.

Tracheids. Resemble wood fibers very closely, cell-walls more porous, ends usually more tapering, always lignified. Typical bast, wood fibers and tracheids are similar as regards the diameter of fibers.

Tracheids with bordered pits: As in the coniferae.

Bast-like tracheids: Ends tapering pointed and comparatively non-porous. These are rarely of diagnostic value.

Ducts or vessels. Always lignified. The following are the types as they occur in vascular bundles:

Porous: The pores vary in form and size. Simple pores, diagonal, cats-eye pores, etc. Widely distributed among plants.

Scalariform: The fern type of duct, sparingly present in other groups.

Reticulate: A modification of the porous type. Very common in dicotyledonous herbs.

Spiral: In herbs and grasses.

Annular: In grasses, less common in other plant groups.

Parenchymatous tissues. The predominating tissue in plant parts or organs. In its typical form the cells are approximately isodiametric, rather thin-walled and rather loosely united, leaving intercellular spaces. The cell-walls are never lignified. The following are the principal types:

Parenchyma proper: Cell-walls thin, cells from isodiametric to somewhat elongated, as in roots, stems, rhizomes, tubers, etc.

Pith: The central tissue of stems, rhizomes, roots.

Bark parenchyma: Cell-walls are frequently suberized. Includes cork tissues.

Endosperm tissue of seeds: Very variable as to thickness of walls.

Fruit pulp: Thin walled, loosely united.

Pericarp parenchyma.

Leaf parenchyma or spongy tissue.

Sieve tubes. Associated with vascular bundles. Typically developed in the cucurbitaceous plants. Of no special diagnostic value.

Crystal-bearing fibers. Widely distributed in barks and in some roots and stems. Typically developed in licorice root, cascara bark, etc.

Laticiferous ducts. Typically developed in figs, in dandelion, in milkweeds, and in other plants.

Resin ducts. As in the bark and wood of pines.

Glands. As in many leaves, such as buchu, eucalyptus, pilocarpus, bay, etc.

Glandular cells. As in mace, allspice, ginger, etc. Usually contain resin and oil.

Atypical cells and tissues. Essentially formative or immature, and of very little diagnostic value. Includes the so-called phloem tissue, cambium, cork cambium, phellogen, conducting cells of the phloem portion of vascular bundles, apical cells, and immature cells generally.

The terminology as it applies to cell-contents such as oils, starches, proteid granules, crystals, etc., is but little confused, and nothing more need to be said about it. There are certain micro-chemical tissue, cell and cell-content reagents, as iodine solution, zinc chlor-iodine solution, hydrated chloral solution, phloroglucin solution, acids, alkalies, etc., which are universally employed. Their preparation and use require no further elucidation.

The skilled micro-analyst has little difficulty in determining the purity and comparative quality of the simple spices, as pepper, allspice, cloves, cinnamon and ginger. However matters are quite different when it comes to the examination of powdered vegetable drugs, compound vegetable powders and vegetable products of unknown composition. A thorough knowledge of and wide familiarity with cell-forms, tissue elements and formed-cell contents is an absolute essential in order that accurately reliable and conclusive results may be obtained and serious confusion may be avoided. Such differences in the reports of findings by micro-analysts as one from time to time comes to notice are in part due to the personal equation, in part due to variable methods and differences in judgment in estimating the quantity of tissue elements present and in part (as already indicated) due to a lack of extensive and intensive experience.

Since only a very few micro-analysts have had the desirable and necessary experience in the critical examination of vegetable drugs it would prove of the greatest assistance to prepare careful descriptions of the microscopical characters of the vegetable drugs official in the United States Pharmacopoeia, such descriptions to include official fineness, the organoleptic characteristics and a brief mention of those negative histologic characters as may prove useful in determining more readily the purity and quality of the drug under examination. These descriptions to serve as authentic guides (rather than as a work of authorative reference) for micro-analysts in federal as well as in state and private pure food and drugs laboratories. The following are submitted as examples of the proposed official descriptions. In this matter the U. S. P. Revision Committee would no doubt welcome a proposition of cooperation, as it is recommended to include a description of the microscopical characters of vegetable powders in the forthcoming ninth decennial revision of the U. S. P.

1. ACONITUM NAPELLUS ROOT.

a. Fineness—No. 60. Class A.*

b. Light brown color.

c. Faint odor; recalling horseradish when moistened.

d. Sweetish, soon very acridly pungent, producing a benumbing effect. Acridity marked in fauces and quite persistent.

e. Histology: Abundant rather thick-walled but otherwise typical parenchyma, filled with starch; few thin-walled, light yellowish-brown, porous mostly rectangular sclerenchyma cells; ducts porous with trace of spiral and reticulate. Starch granules compound, twos and fours and some aggregates (5 to 9); hili centric and distinct in larger granules; single granules 5 to 15 microns; polarizing bands quite distinct, broad and right angled.

Typical (polygonal) thick-walled slerenchyma and bast wanting; practically no trichomes; fibrous tissue (tracheids and wood fibers) sparingly present.

A. Fisheri and *A. variegatum* contain more abundant sclerenchyma (rectangular and often considerably elongated). Sclerenchyma wanting in Japanese aconite. All aconites acridly pungent.

2. ATROPA BELLADONNA, LEAF AND HERB.

a. No. 60. Class B.

b. Rather dull green to greenish brown.

c. Somewhat fragrant; heavy nauseous when moist.

d. Somewhat bitter and pungent.

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* See No. 12 of Summarizing Suggestions at close of this report.

e. Largely negative characters, excepting the leaf parenchyma cells filled with micro-crystalline calcium oxalate and the usually much broken, sparingly present, thin-walled, 3- to 5-celled, simple trichomes; stem tissue abundant; characteristic seed tissue and a few oval elliptical pollen grains.

Acicular crystals, sclerenchyma cells, thick-walled trichomes or thick-walled epidermal cells, wanting.

3. ATROPA BELLADONNA ROOT.

2. No. 60. Class A.

b. Light brownish gray.

c. Nearly odorless—slight soil odor.

d. Sweetish; somewhat bitter and pungent.

e. Abundant typical parenchyma filled with starch; some parenchyma cells filled with micro-crystalline calcium oxalate; fibrous tissue sparingly present. Starch granules simple to compound, 6 to 17 microns; hili distinct, excentric; polarizing bands distinct in direct ratio to size of granules.

There should be comparatively little fibrous tissue; no true bast and no sclerenchyma; no trichomes and no acicular crystals.

An active committee could, within a period of one year, prepare descriptions, as indicated in the examples cited, of all of the official vegetable drugs. To do this it would be desirable to draw upon the work already done by European and American pharmacognosists, verifying and checking the results recorded by a careful reexamination of selected drug samples of known purity.

The organoleptic tests are indeed valuable adjuncts to the microscopical work. There is, however, some variation of opinion regarding the interpretation and valuation which is to be placed on comparisons of color, odor and taste, even among those having had considerable experience and endowed with a fairly normal special sense development. Our color terminology is in great confusion, and so far as the olfactory sense is concerned, there are only comparatively few odors or flavors which admit of ready comparison such as tea flavor, coffee odor, vanilla odor, raspberry flavor, loganberry flavor, and the odor of such drugs as valerian, cubeb, fenugreek, asafetida, aloes, turpentine, camphor, calamus, etc., and the odor of the spices. Our comparative judgment of tastes is more reliable. Much experience is necessary to form fairly reliable estimates of flavors (associations of tastes and odors), though pure fruit flavors are, as a rule, readily distinguishable, as that of apples, dried apples, peach, dried peach, quince and strawberry. Manufactured fruit preparations generally lose much of their flavor due to many causes, as cooking, steaming, fermentative changes, presence of decayed (mouldy) fruits, mixing of several kinds of fruits or fruit juices, etc., to say nothing of the wholly artificial or imitation fruit flavors and so-called fruit products which have little or no fruit in their composition.

We shall give a few tests which have proven especially useful in the examination of drugs and food products. It will be found that many of the test results are largely approximate, and some of them are primarily intended to serve as aids or checks to the chemical examination.

I. METHODS USEFUL IN THE EXAMINATION OF VEGETABLE DRUGS, SPICES, ETC.

1. *Mace Test.* To a pinch of the powdered mace add 10 per cent. sodium hydroxide solution. Banda or true mace changes color only slightly, whereas wild or Bombay mace turns a deep orange color.

2. *Conium Test.* To the substance to be tested for the presence of conium fruits (as anise, caraway or other unbelliferous fruits), add 25 per cent. sodium or potassium hydroxide solution. In the presence of one per cent or more of conium fruits a distinct mouse odor is developed in time (10 minutes to one-half hour). This test is not reliable with old unbelliferous fruits, as many of them develop a more or less marked mouse odor with alkalies.

3. *Lignin Test.* The classic phlorglucin-hydrochloric acid test is useful in making estimates of the amount of lignified tissue present, as in old belladonna root, aconite roots and stems, lobelia herb, fruit products, spices, etc.

4. *Grahe's Cinchona Test.* Drive the moisture from the inner surface of a small test-tube by holding it over a Bunsen burner. Into this dried test-tube place a pinch of finely powdered cinchona bark (No. 80) and heat rather carefully over an alcohol lamp or Bunsen burner. When the bark begins to char, red fumes begin to fill the tube and condense on the side of the tube as a reddish purplish liquid. The intensity of the reaction is approximately proportional (direct proportion) to the percentage of alkaloids present. Some skill and experience is necessary to perform this test well. The tube must not be heated too quickly or too much, and the powder should be uniformly fine.

5. *Beaker Sand Test.* Pour a definite amount of the powdered spice or vegetable drug into a beaker, add water, stir until the sand is washed away from the vegetable particles and settles to the bottom of the beaker. Let a stream of water run into beaker so as to wash out the vegetable matter. The final washing and decanting must be done carefully so as not to lose the sand. Salt brine may be used instead of water, should the vegetable matter have a comparatively high specific gravity. Dry sand and weigh to obtain the percentage of sand present.

6. *Ash Determination.* According to the regulation method. The percentage of the acid-insoluble residue should also be determined. It should be borne in mind that the ash determination gives only approximate results as far as the presence of clay and dirt is concerned, since the organic matter of dirt is combustible. The ash percentage varies extremely in vegetable drugs, especially in herbs and leaves. The sand percentage is comparatively high in those herbs and leaves having abundant trichomes, especially if the drug plants (or herbaceous spices) bearing such trichomes are grown in dry sandy soil. Dirt (and sand) percentage is apt to be high in roots and rhizomes, particularly when rootlets are abundant and when the gathering is carelessly done.

C. H. LaWall and H. A. Bradshaw have prepared a table of ash contents of representative air-dried crude vegetable drugs which will serve as a very valuable guide for micro-analysts, in making ash determinations.

(To be continued)

ON DRUG STANDARDS.

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The present plan of the Pharmacopoeia of making a minimum standard of a drug the real standard for that drug is not a satisfactory plan. To say that because in certain years it is impossible to get very much stramonium, for instance, which will assay 0.25 per cent. of alkaloids, therefore it is necessary to make this lower quality a standard drug, though in other years it is comparatively easy to obtain the drug containing twice this amount of alkaloid, is not a scientific way of setting standards. It is making commercial conditions the basis of scientific usage. It is placing too much emphasis on commercial variations in drug quality.

Commercial variations must, of course, be taken into consideration, for this is