argument, vertigo is not infrequently the consequent of grave organic disease of the central nervous system or of important viscera—notably of the kidney and liver. Aside from the palliative treatment usual in such cases, we may profitably seek to cope directly with the vertigo itself, along the lines already fully indicated. Indeed, it is precisely in such discouraging dilemmas that a rational insight into the true nature of the symptoms will be found most useful.

53 West 38th Street.

DISCUSSION.

DR. A. L. BENEDICT, Buffalo, N. Y., said that while this paper might equally well have been read in the Section on Physiology, it is a very valuable contribution to the study of therapeutics and, therefore, appropriate. He approves of the attitude of the writer as to the organs of special sense. There has been nothing more beautifully demonstrated in physiology than that the semicircular canals are organs of equilibrium. He was astonished to hear the reader of the paper attack the accepted view as to the action of the semicircular canals, and cited, in illustration, a personal experience: Recently, during a journey, he spent part of the night in meditating on the wonderful mechanism of the semicircular canals. When he awoke in the morning he discovered that what he thought was the front of the car was the rear and that the car was going in the contrary direction to that which he had thought. Similar experiments have made him sceptic with regard to the semicircular canals. He thinks that many of our ideas of equilibrium come from the liver. For instance, in going up and down in an elevator, the feeling is referred to just below the diaphragm. He was glad that the lecturer had taken away the old view as to the function of the semicircular canals—it is a beautiful theory, but it is not well substantiated.

DR. W. B. HILL, Milwaukee, Wis., said that the reader of the paper had illustrated the fact that all treatment should be based on physiology, which alone affords a rational basis for therapeutics.

THE PHARMACOLOGIC ASSAY OF DRUGS AND ITS IMPORTANCE IN THERAPEUTICS.*

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NOTE.—The word "pharmacology" is employed as meaning "the study of the changes induced in living organisms by the administration in a state of minute division of such unorganized substances as do not act merely as foods."

After a correct diagnosis has been made, one of the most important questions to be considered by the physician is that of dosage. Especially is this true when, as often occurs, the patient's life depends upon prompt and efficient aid. But if the drugs prescribed are not of fixed and definite strength our efforts may prove utterly unavailing.

Until a few years ago we were obliged to employ pharmacopoeials of uncertain and varying strength. This variation was due not alone to differences in the process of manufacture, but also to the fact that the amount of active constituents contained in the crude drug itself varies from season to season, is modified by habitat, climatic influences, method of collecting, curing, handling, storing, etc. Where the active principles only are employed, the dose can be fixed exactly. In the case, however, of certain important drugs, such as the heart tonics, ergot, etc., a chemical assay is impossible with our present technique, owing to lack of knowledge of the active principles and of their therapeutic value, as well as to the ease with which chemical break-down occurs. Hence

the question arises: "If chemical assay fails to give accurate data relative to the pharmacologic activity of a drug, by what method or methods may such information be obtained?" During the past six years I have been trying to answer this query, and desire at this time to consider briefly some of the methods of pharmacologic assay, the results obtained, and the clinical value of the drugs experimented with.

Of the many theories offered to explain the reactions between the elements of the animal body and drugs, chemical affinity seems the most plausible—the normal function of a given organ being altered in degree by the union occurring between the protoplasm of its cells and the given drug.

It is important in making comparisons of the results obtained from the administration of drugs to animals that the following be kept in mind: Since different species of animals react differently to the same drug, as they do to the same species of bacteria, it is necessary to determine by numerous experiments the type of animal best suited for the assay of each drug.

The animals employed in any pharmacologic test must be as nearly as possible of the same species, age, weight, sex, and general physical condition. The conditions obtaining in the experiments should always be constant as regards environment, food, method and time of administering the drug, length of time for making observations, reading and recording results, etc. Animals, during the time of experimentation, should be kept as nearly as possible in the natural condition. The method of administering the drug should be the one that will allow the greatest rapidity and certainty of absorption and produce the least harm to the animal.

The activity of the tested drug should be compared each time with a standard preparation which represents the active properties of a drug of average quality; the strength of the standard being determined by assaying a large number of samples obtained from different sources.

A sufficient number of animals should be employed in each test to determine the average reaction of a normal animal. Drugs should be given to animals in proportion to their weight and general physical condition. As great care should be exercised in carrying out the several steps of a given assay as in making a chemical determination.

Pharmacologic action is quantitative; in other words, the physiologic processes of the animal body are altered in degree, but not in kind, by the influence of drugs. This fact is more clearly demonstrated in healthy than in diseased subjects, the disease process or processes present often causing great variability in therapeutic results. If we could always get our tubercle cases at exactly the same stage, and if diphtheria always meant the presence of the same number of diphtheria germs, of the same virulency, and producing toxins of the same strength, etc., therapeutics would become more exact, provided our drugs were uniformly active.

Abundant evidence has been adduced to demonstrate the quantitative nature of pharmacologic reactions in normal animals. In some instances the means available for recording pharmacologic changes are more exact than in others, consequently the limits of error will be greater with some drugs than with others.

The reaction upon which to base a pharmacologic assay differs according to the nature of the drug. The minimum fatal dose, the amount of protection conferred against a poison, change in blood-pressure, general or special change in the physical condition, etc.—any one

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of these may be in particular instances utilized to fix the standard of strength.

The following illustrations will demonstrate the reliability of pharmacologic methods as a means of determining the degree of activity possessed by a given drug. At the meeting of the Association in Denver, I gave in some detail a method for assaying strophanthus and the other heart tonics by determining the minimum fatal dose for frogs. Since then I have had abundant opportunity to verify the reliability of the method. Three tinctures of strophanthus of unknown strength which had been colored to exactly resemble each other were recently referred to me for assay. These were numbered 1, 2, and 3. In order to check the results ob-

from investigation of a complaint that a certain shipment of glands from a packing house was not the genuine article. The tracings were obtained from the carotid artery of dogs anesthetized with chlorotone. Microscopical and macroscopical examination showed that the complaint was well grounded, the glands being thymus instead of suprarenal. Here we have an instance of undoubted quantitative reaction from the administration of an animal substance to an animal. The details of this work are to be given in a subsequent paper.

Probably the most complicated of pharmacologic assays is the one with which the medical profession is most familiar. I refer to the assay of antidiphtheric

Fig. 1.—Blood-pressure tracing taken from the carotid artery of a dog anesthetized with chlorotone. The suprarenal liquid was diluted with normal saline solution to 5 c.c. in each instance, and slowly injected into the femoral vein.

tained, three tinctures were prepared from these, as follows:

No. 4 = 5 c.c. of No. 1 + 3 c.c. standard tincture + 2 c.c. alcohol.

No. 5 = 5 c.c. of No. 3 + 3 c.c. standard tincture + 2 c.c. alcohol.

No. 6 = 5 c.c. of No. 1 + 5 c.c. of No. 3.

The following table gives the results reported by my assistants:

No. 1 = 50 per cent. reported strength of standard tincture of strophanthus (standard tincture of strophanthus = 0.00015 c.c., the minimum fatal dose per gm. for test frogs). Mogk.

No. 2 = 100 per cent. standard tincture. Mogk.

No. 3 = 150 per cent. standard tincture. Mogk.

No. 4 = 57 per cent. standard tincture. Actual strength 55 per cent. Variation 2 per cent. Hamilton.

Fig. 2.—Blood-pressure tracing obtained in the same manner as No. 1. Suprarenal liquid solution was, however, more dilute than that employed in No. 1.

No. 5 = 107.5 per cent. reported strength of standard tincture. Actual strength 105 per cent. Variation 2.5 per cent. Mogk.

No. 6 = 100 + per cent. reported strength of standard tincture. Variation less than .5 per cent. Hamilton.

The above table shows that two men assaying tinctures of strophanthus of unknown strength by the use of frogs are able to obtain results showing a maximum variation from the actual strength of only 2.5 per cent. Similar results have been again and again obtained by the application of this method.

Abel and other workers claim that the active principle of suprarenal glands, producing hemostasis when applied to mucous membranes, when injected into the circulation produces marked temporary rise in blood-pressure. That this rise in blood-pressure varies with the amount of extract injected is well shown in tracings Nos. 1 and 2, while tracing No. 3 gives the results obtained

serum by the determination of the smallest amount of serum that will neutralize a given quantity of diphtheria toxin.

The question has been raised as to whether this should be called a pharmacologic assay. It seems to me there is no ground for objection to such a classification, as both the toxin and antitoxin are "unorganized substances which produce changes in living organisms and do not act merely as foods"; moreover, the bouillon containing the toxins formed by the germ is comparable to a tincture of nux vomica or other drug, as both are solutions containing the products of vegetable cells in solution. In the one case we have the products of a plant composed of a great many cells working together; in the other instance the products are formed by many

isolated vegetable cells. The antitoxin also resembles the suprarenal gland extract in that both are the products of animal cells. The medical profession the world over are agreed that antitoxin can only be assayed by experiments upon animals. In standardizing antitoxin by any of the methods now in use, at least three factors cause a variation in the results, viz., variation in the strength of the toxin, which gradually becomes weaker; variation in the strength of the antitoxin, which also gradually becomes less potent; and variation in the reaction of the guinea-pig to the toxin and antitoxin. On the other hand, in pharmacologic assay of plant drugs, only one variable factor is present, the test animal, since, as a rule, the drugs themselves retain their active properties unimpaired for a sufficiently long time to allow an assay to be made.

Other examples might be cited, but surely a careful consideration of the above results should carry convin-

tion to an unbiased mind that it is possible to determine the pharmacologic strength of drugs from their action on the lower animals.

That, in the absence of pharmacologic assay, great variation exists in the strength of certain drugs, has been demonstrated over and over again by the physician at the bedside. One can appreciate the necessity for such an assay if it is remembered that some of the most powerful poisons known belong to the class of drugs which do not admit of chemical assay. Only a short time ago I found three samples of tincture of strophanthus, purchased in the open market, to be of the relative strength of 1 to 3 to 5. Yesterday one digitalin—Germanic—was found twice as strong as the same preparation from a different manufacturer. Tracing No. 3 indicates what might happen in the case of preparations from the suprarenal glands. Many other instances of variation in strength might be mentioned much more startling than these, some of which have been reported previously; but multiplicity of illustrations is not necessary to prove the necessity of employing, as far as possible, drugs that have been chemically

Fig. 3.—Blood-pressure tracing taken from the carotid artery of a dog. No. 1, result obtained from the injection into the femoral vein of a 0.1 c.c. of the extract submitted for assay; No. 2, result obtained from the injection of 0.1 c.c. suprarenal liquid; No. 3, result obtained from the injection of 0.5 c.c. of extract submitted for assay; No. 4, result obtained from the injection of 0.5 c.c. of suprarenal liquid with chloretone.

or pharmacologically assayed in the treatment of disease.

DISCUSSION.

DR. A. B. LYONS, Detroit, Mich., questioned the propriety of discussing a paper when the author was not present to defend it.

DR. LEON L. SOLOMON, Louisville, Ky., said that the paper raises the question on which the Convention for the Revision of the Pharmacopeia, at its last meeting, needed some light. It rejected all formulæ for standardizing by physiologic assay. The chairman of that convention did not think it was possible to standardize drugs by physiologic tests.

DR. LYONS said that he represented the chemical assay of drugs, as his experience had been in this line of work particularly, so that he would not assume to decide on the value of the physiologic assay of drugs. He would, however, state that, generally speaking, there is not a single chemical assay practiced that can give exact valuation of the physiologic or therapeutic effect of the drug in question, except perhaps in the case of opium. He thinks, therefore, that the chemical processes may well be supplemented by physiologic tests. He wishes to be distinctly understood as favoring the supplementing of chemical by pharmacologic tests, and insists that many of the drugs, especially animal extracts, can never be standardized in any other way. He can not understand, therefore, why the convention on revision of the U. S. Pharmacopeia so positively refused to adopt any pharmacologic tests. He said that he would endeavor to have this unreasonable taboo removed in future conventions.

DR. LEON L. SOLOMON, Louisville, Ky., said that it seemed to him that there was some sort of pressure exerted at the pharmaceutical convention against these pharmacologic tests, and that those who were most active by reason of their pressure at former pharmacopeial conventions, by their knowledge of the customs and methods, had succeeded in preventing proper consideration of this subject.

DR. C. T. MCCLINTOCK, Detroit, Mich., said that the physiologic action of a drug is not a question of opinion, but one of fact. In the case of the organic extracts this is the only possible way of proving their activity. Chemical assays may be criticized, but the rise in blood-pressure from the effects of suprarenal extract, for instance, is a matter of demonstration.

THE UNITED STATES PHARMACOPEIA OF 1900.*

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The United States Pharmacopeia occupies a unique position among the pharmacopeias of the world. Its authority is established throughout the country, mainly through the voluntary assent of the physicians and pharmacists of the United States.

It is true that the government is represented in the convention through the Departments of the Army, Navy, and Marine-Hospital Service, and the custom houses recognize the work in their regulations for the admission of drugs into the country; many of our state laws acknowledge the authority of the book by demanding a compliance with its established standards; but the fact remains that the work is not revised or published by the government, but through a representative body of physicians and pharmacists assembled in convention every ten years in the City of Washington.

The thoroughly republican method of reaching the consensus of opinion in both professions, in giving expression of these by the decennial revisions of the book, exhibits one of the best examples of effective submission to authority and is typical of the highest form of citizenship in a modern republic.

European pharmacopeias are government books and have behind them the weight of authority which the laws of the country demand. For many reasons it must be regarded as more than desirable to continue the American method of revision and publication as long as possible, and it is likely that no change will be made so long as wise, conservative and progressive counsels govern the controlling body.

The Pharmacopeia of 1890 was received, not only in this country, but abroad, as a work fully equal to any published in the world, and it is sincerely hoped that the professions of medicine and pharmacy will give to the new committee of revision appointed last month, that loyal support which was so generously extended to the old committees in former years; as is well known, the decennial convention assembled on May 2, 1900, in Washington; delegates were present from every part of the Union. Twenty-eight states were represented by delegates from various medical and pharmaceutical bodies; national organizations were represented through the AMERICAN MEDICAL ASSOCIATION and the American Pharmaceutical Association; while the government sent accredited delegates from the Army, Navy, and Marine-Hospital Service.

Medicine and pharmacy were about equally represented; fifty-seven medical colleges, medical departments of universities and state medical societies sent delegates; while fifty-nine colleges of pharmacy, pharmaceutical departments of universities and state pharmaceutical societies sent delegates.

It will be seen that the convention was a thoroughly representative one; this is further shown by the officers selected to preside over the deliberations, which were

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