of not less than five rats shall be used and at least 60% of the animals injected must survive at least 48 hours from the time of the injection. While these rules were applied to the testing of arsphenamine and neo-arsphenamine, the same methods may be used for determining the toxicity of other drugs.

The results obtained on these animal tests may be utilized in formulating the proper dose, concentration, and solvent to be used in preparation intended for human use.

CLINICAL TESTS.

It is sufficient to state, however, that in spite of careful physico-chemical and biological considerations, the real proof of a good, stable, potently therapeutic, comparatively non-irritating and non-toxic pharmaceutical preparation lies in the end results, and these are satisfactory clinical tests. Therefore, the work of a laboratory must be so planned as to coördinate the manufacturing, chemical, biological and clinical facts.

In conclusion, then, sterile pharmaceutical preparations can be elevated to a higher scientific place by the application of known physical and chemical principles to physiological processes.

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ORGANOTHERAPEUTICS FROM THE PHARMACIST'S STANDPOINT.*

BY DAVID KLEIN, PH.D.

The administering of gland desiccations and derivatives is a comparatively new branch of therapeutics. Interest in this field, on the part of physicians, is increasing rapidly, with a resulting increase in the number and brands of products that are being offered to the practitioner and to the pharmacist. Concise information concerning the source and manufacture of the various glandular derivatives is not readily available; yet the intelligent purchasing, handling and dispensing of these products must be based upon such knowledge. It is with the hope of clear-

* An address without notes on the above subject was delivered before the Chicago Branch of the American Pharmaceutical Association, March 10, 1922. This paper follows closely the subject matter of that address, although a portion of it, centering around the gland specimens displayed at that time, must obviously be omitted.

ing up some of the confusion that must exist in your minds, that I venture to address you on this subject.

The terminology in this field is neither standardized nor accurate. The products are variously referred to as endocrines, hormones, autacoids, ductless glands, enzymes. The first term is to be preferred, if we are to have due regard for previously recorded phenomena and their names. For instance, the word "hormone" has definite significance in connection with the mode of action of enzymes, and has been demonstrated in certain cases. It has not been shown that all gland actions are hormonic in character. Our knowledge, in fact, of the active principles of the glands, their formulas and properties is very, very meager.

What is known in this field has been accumulated through clinical observations, and biological experiments; the chemical aspect of the subject has been undeveloped and remains as a highly attractive problem. It was through the correlations of thyroid dysfunction and cretinism, myxedema and goiter, of suprarenal dysfunction and Addison's disease that interest in organotherapeutics was awakened. Later the work of Brown-Sequard on testicular extracts added greater impetus to study in this field, and we may say that modern organotherapy dates from the publication of his papers in 1889. Since then, there has grown up a vast literature, which is being added to at a very rapid rate. It would take us too far afield to discuss in detail all the glands included in the term "endocrines" and their functions. The prominent ones are the pituitary, pineal, thyroid, parathyroid, thymus, suprarenal, ovary, testes, mammary, placenta.

These glands profoundly influence the physical and mental status of the individual. Thus, dwarfism is related to hypofunctioning of the anterior pituitary lobe; giantism, to hyperfunctioning of the same organ. Too little thyroid activity produces as extreme types the cretin, and the myxedematous individual; too much thyroid, the exophthalmic goiter. The posterior pituitary body contains a something which can raise blood pressure, and presumably a something else which contracts involuntary muscle. Advantage is taken of the latter property in the use of pituitary extracts in obstetrics and pernicious constipation. The suprarenal medulla contains a chemical compound having the property of raising the blood pressure by constricting the blood vessels. This substance, epinephrin, is the only case of isolation of the active principle in pure form from any of the endocrines. From one other case, the thyroid, a very iodine-rich substance has been prepared, which Kindall believes is the active component of the thyroid. The sexual organs have other than reproductive properties, which influence the manifestations of those characteristics which are usually associated with either sex. The profound changes resulting from castration are common knowledge.

The above are but a few examples of glandular influence. Time will not permit of further discussion of the functions of the various glands, yet it is upon the clinical evidence thus collected that glandular medication is founded. Such treatment presupposes:

1. That the ailment is due to improper endocrine function.
2. That the malfunctioning can be corrected by giving the proper endocrines.
3. That the active principles in the endocrines of animals are effective for man.

Opinion differs as to the method of administering the gland products. Some hold that, excepting certain glands, such as the thyroid, oral administration is ineffective. Others offering clinical evidence maintain that administration by mouth is valuable and proper. Still others argue for hypodermic administration, either intramuscular or intravenous. The whole question presents one of the lively problems of organotherapeutics. Moreover, we know that the endocrines possess antagonistic and synergistic properties; that the action of one gland may be repressed by another and increased by a third. This has led to a pluriglandular therapy, which has for its basis this hypothesis—the cells of the body are able to pick out of the blood stream those endocrine principles in proper amounts that it needs for normal functioning, and to pass up the rest. This hypothesis has led to many bitter arguments among physicians pro and con. You probably are not so much interested in these discussions as you are in the practical consequences. There are many brands of pluriglandular preparations on the market, under simple and also very complex names. Your problem is how many of these to carry, how to give service to the patient upon the physician's prescription, especially when there is no specification.

Turning then to the practical side of organotherapy, there will be found on the market, the desiccated glands in powdered form, in capsules, in tablets, both plain and coated, and in pluriglandular mixtures. Besides these, there are ampuls of liquid extracts of some of the glands. A little later I shall take up the methods of preparation, but here I wish to emphasize that no matter what the form may be, these glandular derivatives are essentially meat products, dried meat powders, if you please, and must be handled accordingly. Moisture and warmth are conducive to spoilage. Glandular products should be kept in tightly covered containers and in a cool place, away from direct sunlight. Our information is very meager regarding the deterioration with time of glandular powders and tablets. In this case, as in others, where there is a lack of information, our advice is to play safe, not to overstock but to buy more frequently from as fresh sources as possible. The liquid extracts are usually dated, if they deteriorate with time.

Let us now consider raw material and methods of manufacture. They are all important factors in establishing the quality of the finished product, and as such are worthy of careful scrutiny by you. The animals from which the glands are derived are the food animals, *viz.*, cattle and hogs and sheep. Since these are handled in largest units by the meat packing companies, it follows that the biggest proportion of raw glands comes from the big meat-killing centers.

Moreover, since the quality of the finished product can be no better than the raw material, special consideration must be given to the proper handling of the glands as soon as they are removed from the animals, in order that the glands may be maintained in as fresh a state as possible. Transportation difficulties make it desirable to work up the glands close to the source of supply; hence, the advantage in raw material that is enjoyed by the packers.

There are different methods of desiccating the raw glands. One largely used is to grind the material in a meat chopper, spread it thin on trays or pans, and dry in a vacuum dryer at a low temperature. Very little is known regarding the stability of the active principles at temperatures above that of the body; it is good procedure to regulate the driers so that the glands do not attain a temperature

above 98° F. until dry. There is a great divergence among manufacturers on the point of temperature.

Many of the dried glands will powder without defatting, but some of them contain too much fat to grind up successfully. These must be defatted. The matter of the solvent to be used is of prime importance. There is little known about the effect that different solvents have upon the potency of the finished product. At any rate, the amount and composition of the material taken out by the solvent differ markedly. As a general rule, the glands that are not defatted are to be preferred, in the present state of our knowledge. At all events, the desiccated material is ground and sifted to remove fibrous material. The number of pounds of raw material to make one pound of finished powder varies with the different glands. Thus a ratio of 1.: 5 means that five pounds of raw glands were required to make one pound of finished powder. It is exceptional for a gland to dry down in a smaller ratio than 1 : 5, so that any product bearing a smaller ratio is to be regarded as having been diluted. The exceptions are certain U. S. P. products, which must be diluted to conform to the standards.

Some confusion exists with regard to the expression of amount of glands contained in tablet, capsule or ampul. Certain pharmaceutical houses express the amounts of glands present, on the basis of the raw glands used in making the desiccation, while others state the amount of dried glands used. Each system has its advantages. A combination of the two is to be preferred; that is, expression of the amount in terms of dry gland, but with a supplementary statement of the equivalence in raw glands. Thus "Thyroid 2 grain. This tablet contains desiccated thyroid gland equivalent to 10 grains of fresh gland." It might be of some interest to know the number of glands required to make a pound of fresh or dried product. It takes about two hundred pituitary glands to make a pound of fresh glands and about one hundred pounds[1] of raw glands to make one pound of desiccated, defatted posterior lobe. About six hundred cow ovaries are needed to make up one pound of dried gland, and a considerably greater quantity of hog ovaries are required for a pound. At the present time, demands are very close to the available supply of pituitaries and ovaries. With the demand for these products rapidly increasing, it is not easy to foresee how the requirements of the medical profession will be met. Relief can only come ultimately through greater production of animals or through the synthesis of the active principles of the glands; in view of our present state of knowledge of the chemical composition of these substances, immediate relief through synthesis is not to be even thought of.

In closing, I should like to emphasize the source and perishable nature of glandular derivatives, the necessity of keeping them in a cool, dry place, the desirability of frequent renewals of stock to insure fresh preparations, and finally the soundness of raw glands and methods of desiccating as factors that make for quality.

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[1] This amount will vary depending upon the way the glands are trimmed at the abattoirs.