

ENDOCRINE PRODUCTS.*

BY PAUL S. PITTINGER.

The discovery of the importance of internal secretions has led to extensive clinical trials with preparations of the so-called ductless glands, and other tissues which elaborate, or are supposed to elaborate such internal secretions.

The most commonly known preparations of this type are the desiccated powder, tablets and sterile solutions of the extracts of the following:

Suprarenal Gland	Ovarian Residue
Epinephrin	Parathyroid Gland
Whole Pituitary Gland	Testicular (Orchic Gland)
Pituitary Posterior Lobe	Mammary Gland
Pituitary Anterior Lobe	Thymus Gland
Whole Ovarian Gland	Pineal Gland
Corpus Luteum	Thyroid Gland

Some of these have shown decisive therapeutic results; *viz.*, Thyroid, Parathyroid, Suprarenal and Pituitary Glands, Whole Ovary, Corpus Luteum and Ovarian Residue.

The Desiccated Pituitary Body, Solution Pituitary Body, Desiccated Thyroids, and Desiccated Suprarenal are official in the U. S. P. IX.

The rapidly increasing importance, and the demands for this class of preparations prompted me to read a paper on the subject of "Endocrine Products" at our last Department Manager's Meeting.

A few days after this meeting Dr. Stewart informed me that he had suggested I be invited to present a similar paper before the Philadelphia Branch of the A. Ph. A. That is my excuse for being here to-night. I trust, therefore, I will be able to make the subject not only instructive but interesting by illustrating my remarks with actual specimens of the fresh glands, method of dissecting, and the various products manufactured from each.

We will first consider each gland or organ individually and later consider them collectively.

Products of the Suprarenal Gland.

The Suprarenal Gland, or Capsules in man lie in contact with and immediately above each kidney. The gland is enclosed by a connective tissue capsule which is continuous with the connective tissue of the gland.

The average dimensions of each in man are:

Height 27 mm.

Breadth 47.5

Thickness 4.5 mm. (Except at the base where they are twice this size.)

They are usually larger in the female than in the male. The weight averages 4½ Gm., but they exhibit considerable variation in size and weight.

The Suprarenal Gland from cattle is about 34 mm. in height, 47 mm. in breadth and about 12 mm. in thickness.

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Each Suprarenal consists of two parts; *Cortex and Medulla*, which although anatomically united in most vertebrate animals, are morphologically distinct and are developed from different embryonic formations.

Uses.—From the medulla or the inner portion of these glands, epinephrin is obtained (See Solution Epinephrine). The cortex or outer portion of the gland is essential to life and has some important relation to the maintenance of normal muscular tone, normal functioning of the reproductive system, and the anterior portion of the brain, including the pituitary. Preparations of the cortex or of the whole gland have been given in treatment of extreme muscular weakness, in amenorrhea, and in the treatment of Grave's disease (exophthalmic goiter).

Desiccated Suprarenals is prepared from Suprarenal Glands of animals which are used for food by man, cleaned, freed from fat, dried and powdered. It contains not less than 0.4%, nor more than 0.6% Epinephrin, the active principle of the suprarenal gland.

One part of the dried Suprarenal represents about 6 parts of the fresh glands free from fat.

Assayed biologically, one gram of dried Suprarenals contains the equivalent of 10 mgm. of laevo-methylamino-ethanol-catechol.

Epinephrin is the isolated purified active principle of the medulla of the Suprarenal Gland physiologically standardized.

Solution of Epinephrin.—The usual commercial solution is made by dissolving one part of Epinephrin in 1,000 parts of acidulated water, the acidity accurately adjusted by means of a potentiometer, preservative added, and physiologically standardized. The solution is preserved by saturating the solution and excess space in the bottle with carbon dioxide gas to retard oxidation.

Solutions of Epinephrin have largely replaced solutions prepared from the official desiccated Suprarenals. They have many advantages over the latter in that they may be made of definite strength and are less liable to bacterial infection and decomposition.

Uses.—It has a marked effect on involuntary muscles, particularly of the blood vessels, causing rapid rise in blood pressure; indicated in shock; surgical heart failures, collapse from hemorrhage; in asphyxia, in asthma, and as an antidote to Insulin in treating "Insulin shock."

Glycerin Extract Adrenal Cortex.—This preparation is made by carefully removing all extraneous tissues and the medulla from the Suprarenal Gland, finely mincing the Cortex and rubbing it up in a mortar with definite amounts of glycerin.

Products of the Pituitary Gland.

The Pituitary Body is situated at the base of the brain lying in the *Sella Turcica*. In man it weighs about $\frac{1}{2}$ gram. It is connected with the brain by a funnel shaped stalk, the Infundibulum. On account of a natural cleft which runs across the gland in an oblique plane it is an easy matter to split it into two portions; Anterior and Posterior Lobe.

The gland most commonly used in therapeutics is that obtained from the ox. It is about $\frac{3}{4}$ -inch in diameter. The smaller, or Posterior Lobe forms only about 10–15 per cent. of the total gland. The total gland contains about 80% of water, or

in other words, 100 parts of fresh gland give about 20 parts of dried substance containing 2-3 parts of the Posterior Lobe.

Uses.—*Anterior Lobe.*—The Anterior Lobe of the pituitary gland gives off a growth-controlling secretion which influences normal development. The preparations of the Anterior Lobe are used (*a*) for enuresis (*b*) for the regulation of growth, especially of the pelvic organs and correction of menstrual irregularities in young women and in certain types of amenorrhea and dysmenorrhea, (*c*) to promote the development of the bones and the process of calcification, (*d*) for the relief of symptoms in women at the time of the menopause (*e*) for its possible effect in delaying degenerative changes in elderly persons and (*f*) pituitary obesity.

Posterior Lobe.—The Posterior Lobe produces a smooth muscle stimulant, a very powerful agent which has been found useful in (*a*) dyspnea, (*b*) the polyuria of diabetes insipidus, (*c*) flatulence (not due to obstruction) (*d*) post-operative paralytic ileus (*e*) to stimulate the contraction of the uterus in so-called third stage of labor, and (*f*) to control atonic hemorrhage and induce contraction of the uterus after labor. Ineffective by mouth.

Desiccated Whole Pituitary Gland.—This is prepared by freeing the Pituitary Glands of cattle from all extraneous tissues, grinding, drying and powdering.

Desiccated whole Pituitary corresponds to 5 parts of the fresh whole gland.

Desiccated Posterior Pituitary Body.—This substance is prepared by carefully dissecting out the Posterior Lobe, grinding, drying and powdering.

One part desiccated Posterior Body corresponds to 6 parts of the fresh Posterior Body.

Desiccated Anterior Pituitary Lobe.—This product is prepared from the Pituitary Body after removing the Posterior Lobe and all extraneous tissues. The gland is then ground, dried and powdered.

One part of the desiccated Anterior Lobe corresponds to 5 parts of the fresh Anterior Lobe.

Pituitary Extract.—This preparation is prepared from the Posterior Lobe of the fresh Pituitary Gland. The carefully dissected Posterior Lobes are finely minced, macerated in acidulated water, strained, and carefully freed from albuminous and other inert substances, a small amount of preservative added, candle filtered, physiologically standardized, ampuled and sterilized.

Solution Anterior Lobe Pituitary.—This preparation is prepared from the Anterior Lobe after carefully removing the Posterior Lobe. The ground, fresh gland is macerated in acidulated water, freed from all inert substances, a small amount of preservative added, candle filtered, physiologically standardized, ampuled and sterilized.

Products of the Ovary.

The ovary, one on either side of the body, is the sexual gland proper, within, and from which are developed and liberated, the mature, maternal, sexual cells, the ova.

They are two nodular, oval-shaped bodies of an elongated form situated one on either side of the uterus in the posterior layer of the broad ligament, behind and below the Fallopian tube. They are of a grayish pink color and present either a smooth or a puckered, uneven surface. In humans they are about $1\frac{1}{2}$ -inches in length, $\frac{3}{4}$ -inch in width, and about $\frac{1}{8}$ -inch thick, and weigh from 1 to 4 grams.

The glands used in therapeutics are those from the cow which are approximately 2-2 $\frac{1}{2}$ -inches in length and $\frac{3}{4}$ -1-inch in diameter.

Uses.—Whole ovary preparations are most useful in disturbances (a) of the natural menopause, (b) of the surgical menopause, and (c) in the late establishment of menstruation.

Corpus Luteum is indicated in functional amenorrhea or scanty menstruation, dysmenorrhea (painful menstruation) of ovarian origin, sterility (not due to pyogenic infection or mechanical factors), and in excessive vomiting of the early months of pregnancy and in certain disturbances of the menopause.

Ovarian Residue preparations are said to be of use.

- (1) in the late development of puberty
- (2) infantilism
- (3) in menorrhagia
- (4) obesity and amenorrhea

The ovarian preparations are used for the treatment of a number of nervous symptoms including dizziness, sleeplessness, headache, muscular pains, asthma, etc., which are common at the natural menopause.

Desiccated Whole Ovarian Gland.—The whole Ovarian Gland of cattle is used, including the Corpora Lutea, selected, freed from extraneous matter, dried and powdered.

One part of the desiccated gland represents 7 parts of the fresh whole ovary.

Solution Whole Ovarian Extract.—This preparation is prepared by macerating ground whole ovary, including the Corpora Lutea, in acidulated water. The mixture is freed from albuminous and other inert substances, strained, a small amount of preservative added, filtered, physiologically tested, ampuled and sterilized.

Corpora Lutea.—This product is formed by proliferation of the Follicular Epithelium which remains after extrusion of the ovum and by the ingrowing into the follicle of the so-called Theca cells and blood vessels. The fully-developed Corpus Luteum in most animals consists of cells arranged in trabecula converging toward the scar which formed at the place where the follicle had burst.

The luteal cells as they are called are characterized by containing considerable quantities of lipoids.

Desiccated Corpora Lutea.—This preparation is obtained by carefully dissecting from the ovary, the Corpora Lutea, grinding, drying and powdering. One part of the desiccated gland represents 6 parts of the fresh Corpus Luteum.

Solution Corpus Luteum Extract is prepared by extracting the Corpus Luteum with acidulated water or alcohol. The solution is then freed from inert substances, a small quantity of preservative added, candle filtered, physiologically tested, ampuled and sterilized.

Desiccated Ovarian Residue.—This product is prepared from the part of the ovary which remains after the Corpus Luteum has been removed. All fat and other extraneous tissues are removed, the gland ground, dried and powdered.

Each part of the desiccated powder represents 4 parts of the fresh ovaries after the Corpora Lutea has been removed.

Solution Ovarian residue is prepared by extracting the ovarian residue with acidulated water and straining. The solution is then freed from albuminous and

other inert substances, a small amount of preservative added, filtered, tested physiologically and sterilized.

Liquor Folliculi is the name applied to the solution contained in the ovarian follicles.

Thyroid Gland.

This organ is situated in the neck in front and at the sides of the trachea. It is yellowish red in color with a fibrous capsule which generally takes the form of two lobes situated on either side of the larynx and windpipe, united by an isthmus over the trachea.

The isthmus in humans is from 5 mm. to 2 cm. in breadth. The height of the lateral lobes ranges from 3 cm. or less to twice as much within normal limits. The transverse diameter of the whole organ is 6-7 cm.

The weight is about 1½ ounces with wide variations. The isthmus varies much in size and is often more or less incorporated in one of the lobes. In 10% it is absent.

Uses.—The thyroid gland stimulates metabolism and maintains immunity against infectious agencies and acts as a sort of balance wheel in maintaining the proper relative functions of the other glands. It is specific in the treatment of cretinism, myxedemia, goiter, Grave's disease and similar disorders. It is also indicated in obesity, tetany, epilepsy, eclampsia, etc.

Desiccated Thyroid.—The Thyroid glands of animals which are used for food by man are freed from connective tissues and fat, dried and powdered, and contain not less than 0.17%, nor more than 0.23% of iodine in thyroid combination.

One part of dried thyroids corresponds to approximately 5 parts of fresh glands. This proportion, however, is not constant in view of the fact that the powder is standardized to a definite iodine content.

Solution Thyroid Extract is prepared by macerating the ground thyroid glands in acidulated water and straining. This solution is freed from albuminous and other inert substances, a small amount of preservative added, filtered, ampuled and sterilized.

Parathyroid Glands.

These organs, the "Epithelial Bodies" of many authors are, small elliptical masses situated near the Thyroid which formerly were mistaken either for accessory thyroids or for lymphatic nodules. They arise from the posterior wall of the 3rd and 4th pharyngeal pouches, and thus differ from the thyroid body in origin as well as in structure.

In humans they are 6-7 mm. long, 3 or 4 mm. broad and 1.5-2 mm. thick. They are always separated from the thyroid by the capsules. Most frequently the parathyroids exist as two pairs on each side. Their disposition, however, may be "asymmetrical;" in some cases as many as 4, in others none, lying on one side.

In many animals (dog, cat, rabbit, monkey) the upper parathyroid is deeply imbedded in the substance of the thyroid, (but never in man) and it has on that account been termed the "Internal" Parathyroid, the lower being designated "external."

The expression "Parathyroid III" and "Parathyroid IV" to indicate the Visceral pouch which gives origin to each gland, are on the whole the least ambiguous and should therefore be employed.

Uses.—A mixture of the thyroid and parathyroids with calcium lactate is useful in the treatment of rhinitis, hay fever, asthma, sprue, chronic ulcers, and many other conditions of disturbed calcium metabolism.

Desiccated Parathyroid Glands are prepared from the exterior parathyroids of the ox, freed from fat, cleaned, dried and powdered without the addition of preservative or diluent.

One part of the desiccated parathyroid corresponds to 10 parts of the fresh gland.

Thymus Gland.

The thymus is apparently an organ of service to the nutrition, possibly blood formation, of the foetus and infant, since it usually reaches its greatest size at about the end of the 2nd year, having grown since birth fairly in proportion to the body. It is therefore a temporary organ attaining its full size at the end of the 2nd year, when it ceases to grow, and remains practically stationery until puberty, at which period it rapidly degenerates. It does not entirely disappear, for the shrunken and degenerated mass, even later in life, maintains a likeness to the original form, and retains within its substance, small portions of thymus tissue.

The gland is developed from outgrowths of the third branchial pouch on either side, which, meeting in the midline, unite to form a solid block of cells, this later becoming hollowed out and branched. It extends from the level of the fourth costal cartilage upward as high as the lower border of the thyroid gland.

The average weight of the human thymus at birth is about 10 grams. It is heaviest about puberty and its average weight is about 35 grams. The gland most commonly employed in therapeutics is that of the calf or sheep.

Uses.—Thymus Gland has been used in many pathological conditions, including exophthalmic goiter, delayed development, rheumatoid arthritis, osteomalacia, rickets, menorrhagia and metrorrhagia, leucocythaemia, chlorosis and anaemia, haematemesis, haemophilia, osteoarthritis and obesity.

Desiccated Thymus Gland is prepared by removing all fat and other extraneous tissue, grinding, drying and powdering, without the addition of diluent or preservative. One part of the desiccated thymus corresponds to 5 parts of the fresh gland.

Solution Thymus Gland is prepared by macerating the ground Thymus Gland in acidulated water and straining. This solution is freed from albuminous and other inert substances, a small amount of preservative added, filtered, ampuled and sterilized.

Pineal Gland.

The Pineal Body is an outgrowth which is not regarded as an important neural ingredient of the human brain and is generally believed a rudimentary relic, the functions of which are obscure. It is a cone-shaped organ formation 10 mm. in length attached to the posterior extremity of the roof of the 3rd ventricle.

It is slightly compressed from above downward and rests with its apex pointing backward on the dorsal aspect of the mid-brain in the triangular pineal depression between the posterior corpora quadrigemina.

Uses.—This gland has some influence on the growth of the body and the development of the mentality. It is used in treatment of undersized and mentally backward children. (But not mongols or cretins.) See Thyroid.

Desiccated Pineal Gland.—The Pineal Glands of cattle are freed from all extraneous tissues and powdered without the addition of diluent or preservative.

Mammary Gland.

The Mammary Glands used in therapeutics are usually from the sheep. Each gland is approximately 3 inches long x 1½ inches in diameter and weighs about 2 ounces.

Uses.—This gland possesses a marked stimulating action upon the uterus. It has been used in uterine hemorrhage attending metritis, thus counteracting inflammation; it is used in so-called third stage of labor, and to control atonic hemorrhage and induce contraction of the uterus after labor. Ineffective by mouth.

Desiccated Mammary Gland is prepared by freeing the Mammary Gland of sheep from all extraneous tissues, drying and powdering, without the addition of diluent or preservative. One part of the desiccated gland corresponds to 10 parts of the fresh gland.

Solution Mammary Extract is prepared by macerating the ground Mammary Glands in acidulated water and straining. This solution is freed from albuminous and inert substances. A small amount of preservative is added, filtered ampuled and sterilized.

Testicular (Orchic) Substance.

The glands commonly employed in the manufacture of commercial preparations are those from the hog and cattle and vary considerably in size and weight. The testes of the bull average about 3 inches in length and 1¾-inches in diameter.

Desiccated Orchic Substance is prepared by removing all extraneous and connecting tissue, grinding, drying and powdering without the addition of diluent or preservative. One part of the desiccated gland corresponds to 10 parts of the fresh gland.

GENERAL PRINCIPLES INVOLVED IN THE MANUFACTURE OF ALL GLANDULAR PRODUCTS.

Selection.—All glands must be carefully selected as to quality, identity and freshness, *e. g.*, ovaries and Pituitary Gland from cattle, Mammary Gland from sheep, etc.

Storage.—Glands must be frozen solid immediately after their removal from the animal and kept in Cold Storage rooms until used. These Cold Storage rooms should be maintained at a temperature of 5–15° below zero, Fahrenheit. The glands should be placed in Cold Storage even though they are to be used within 3 or 4 days from the time they were taken from the animal.

All glands should be used as quickly as possible after removal from the animal and not kept in Cold Storage for a prolonged period.

Trimming.—Each individual gland must be carefully trimmed free from fat and all extraneous tissues.

Dissecting.—Pituitary Glands. The Posterior Lobe from each individual gland must be carefully separated from the Anterior Lobe by someone trained to distinguish the difference in structure of the two lobes.

Corpus Luteum and Ovarian Residue.—In the preparation of these two products each individual ovary must be cut open and the Corpus Luteum carefully dissected out, leaving the ovarian residue.

Drying.—The least possible amount of heat must be used in drying this class of products owing to the fact that in many cases heat destroys their activity. Most of the drying should therefore take place in air dryers without heat, the final traces of moisture being removed in temperature-controlled warm air dryers and low temperature high vacuum dryers. The air dryers without heat have a distinct advantage over the vacuum dryer in that they dry the gland at temperatures below the fermentation temperature. Most vacuum dryers operate at about the fermentation temperature which should be avoided.

Removal of Fat.—All fat adhering to the exterior surface of the glands should be carefully removed before the glands are ground. It is still an open question, however, as to whether or not the removal of the fat from the powdered gland removes activity. Many workers are of the opinion that the removal of fat from Corpus Luteum, for example also removes activity. In view of the present status of the testing of these substances there is no method of proving whether or not this is the case.

Therefore, no one can prove that the removal of the fat removes physiologically active substances, and on the other hand, no one can prove that products from which the fat has been removed are not as valuable as ones in which it has not been removed.

The concensus of opinion, however, is that the fats should not be removed. This opinion is based upon the fact that practically all fat solvents will also dissolve lipoids which are in many cases active constituents. For this reason fats which are removed should be removed by mechanical methods rather than by chemical methods, or the use of solvents.

Standardization.

All known methods of standardization should be employed.

Products of the Posterior Pituitary are tested and standardized according to their power to produce contraction of the isolated uterus of the virgin guinea-pig, as compared with the contraction produced by a standard.

Products of the Anterior Pituitary, are tested for their effect upon the blood-pressure of rabbits. These preparations produce a fall in blood-pressure and an increase in the amplitude of the tracing of the heart beat.

Products of the Suprarenal Gland are standardized for their power to increase the blood pressure of anaesthetized dogs as compared with a standard.

Products of the Ovary are tested for their effect upon the vas deferens and the isolated uterus.

Thyroid and Parathyroid Glands are chemically tested for combined iodine.

Sterilization.

In view of the fact that heat destroys the activity of some of the solutions of the glandular extracts, some of them cannot be ampuled and autoclave sterilized.

It is therefore necessary to sterilize these preparations without heat by passing them through a candle filter and testing the filtered solution for sterility.

Having thus proven that the bulk solution is sterile, it is filled in sterile rooms with sterile apparatus into sterile containers.

In order to check whether or not the filling operation was accomplished without contamination, it is necessary to subject a certain percentage of the filled containers to a sterility test.

NUMBER OF FRESH GLANDS REPRESENTED PER 100 LBS. DESICCATED GLANDS.

I thought it would perhaps be interesting to say something in reference to the number of fresh glands, and incidentally the number of animals required to produce 100 lbs. of desiccated powder of some of the more important glands.

Pituitary Posterior Lobe.—As stated above, 6 parts of the fresh gland are required to produce one part of the desiccated gland. Therefore, 100 pounds of the desiccated powder require 600 pounds fresh Poster Lobe. These lobes average 100 to the ounce, or 960,000 in 600 pounds.

In other words, the Pituitary Glands from 960,000 cattle are required to produce 100 pounds of the desiccated powder.

Pituitary Whole Gland.—Five parts of the fresh gland are required to produce one part of the dried. Therefore, 500 pounds of fresh gland will be required at an average of 240 to the pound or 120,000 glands. One hundred and twenty thousand cattle are necessary to produce a sufficient number of glands to make 100 pounds of the desiccated product.

Corpus Luteum.—Since one part of the powder represents 6 parts of the fresh gland, 600 pounds of fresh Corpus Luteum are required to yield 100 pounds of powder. As the Corpus Luteum only represents about 33% of the whole ovaries, 1800 pounds of ovaries would be required at an average of 75 to the pound or 135,000 ovaries. In other words, 135,000 cattle are required to produce 100 pounds of this product.

Note: The above talk was followed by a practical demonstration of the effects of Epinephrin and products of the Suprarenal gland on the blood pressure of a dog, with details as to the employment of these reactions as a means of standardization.

The action of Pituitary Extract on the isolated uterus and the methods of standardization were also demonstrated.

The members of the Branch were then conducted through the Endocrine Department where the dissecting of glands on a large scale was demonstrated.

Next the manufacture of Insulin including the working principles of the various apparatus, which was in operation, was described.

LABORATORIES,
H. K. MULFORD Co.,
PHILADELPHIA.
