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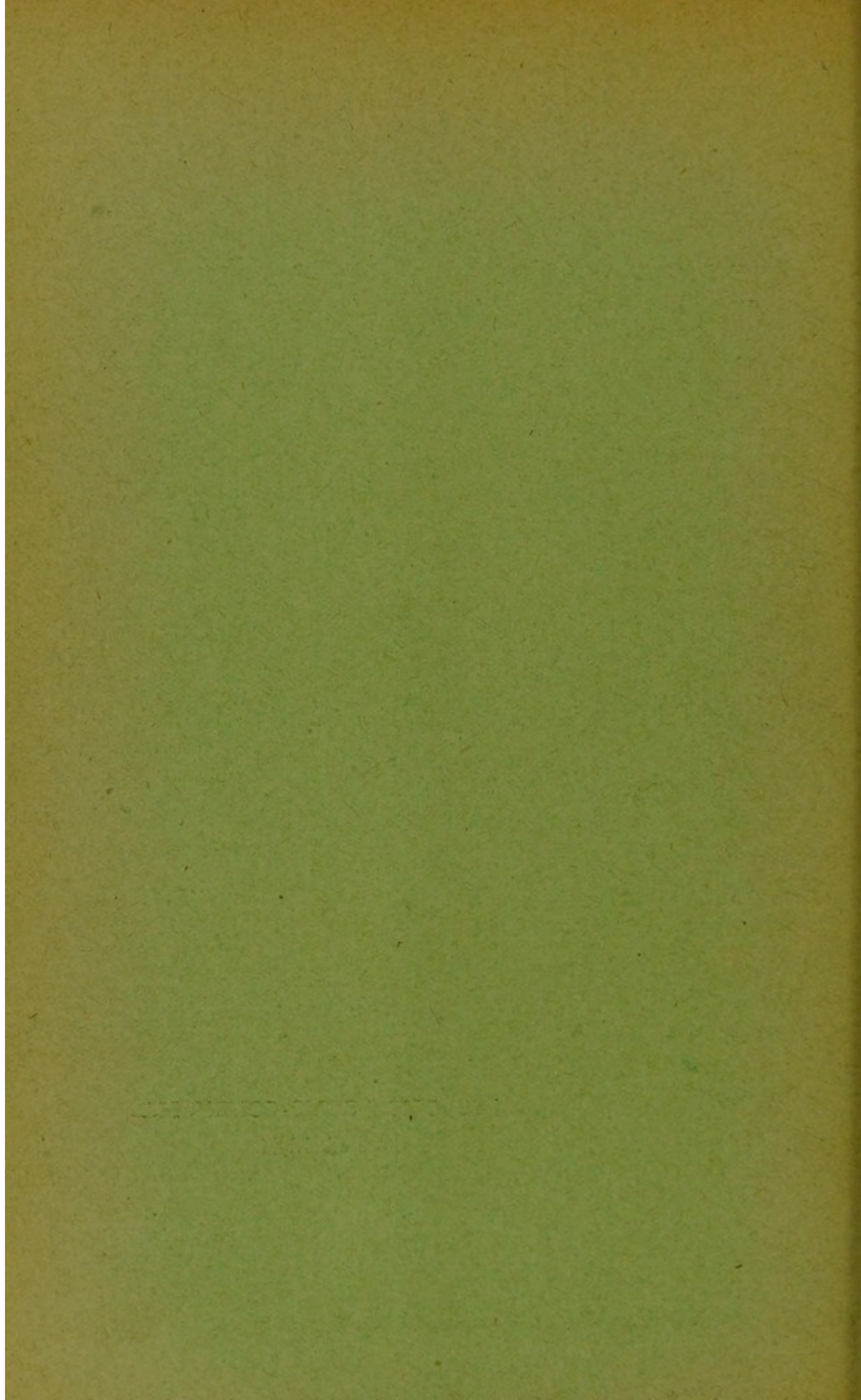
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THE THERAPEUTIC USES
OF THE THYMUS GLAND



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THE THERAPEUTIC USES OF THE THYMUS GLAND.*

SOLOMON SOLIS-COHEN, M.D.

PHILADELPHIA.

Mr. President and Gentlemen: It is always a pleasure to meet my colleagues of the New York County Medical Association. I only regret that what I have to offer for your consideration is not very satisfactory. If at the close of my remarks you shall think that they have been vague and inconclusive, even contradictory, I shall have left on your minds a truthful picture of the state of our knowledge concerning the subject on which you have honored me by asking me to address you.

THYMIC DEATH.

It has long been known that children are liable to sudden death, attributed in some mysterious way to enlargement of the thymus gland. Authors have written learnedly on the subject, explaining, or rather failing to explain, these cases. In his classic study on diseases of the thymus gland, your honored fellow-townsmen, Dr. A. Jacobi,¹ points out how a slight increase in bulk of the tissues occupying the comparatively small space of the mediastinum may produce fatal compression of the trachea.² But why should the thymus suddenly enlarge to this fatal point? Some writers attribute the symptoms of thymic asthma to toxemia, whether from hyperthymization or hypothyminization. But, again, why this sudden change in the secretory activity of the gland?

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Whether these cases are really examples of disease of the thymus or of an unfortunate effort of nature to overcome some other disease, I, at least, do not know. The function of the gland will have to be better known before we can decide; and until we know both the physiology and pathology of the organ better than we now do, we shall lack a sure basis for thymic therapy.

CONTRADICTORY OBSERVATIONS AND DIVERSE PREPARATIONS.

Clinically, too, we are confronted with the contradictory reports of equally competent observers upon the therapeutic action of the thymus gland in various cases of disease. One reason for this is to be found in the very varying nature of the preparations administered. In the beginning the fresh glands of recently slaughtered animals were used. Later, commercial preparations—desiccated powders, tablets, glycerin extracts and solid extracts—have been employed.

I wrote to the leading manufacturers of America and England in order to get some idea of the manner in which the preparations on the market are made. Messrs. Burroughs & Wellcome, to my surprise, excused themselves from replying to my query. Messrs. Parke, Davis & Company said they used only the glands from sheep, usually young ones, such as the butchers sell for sheep, usually young ones, such as the butchers sell for lamb. Messrs. Armour & Company said that the glands were taken from calves, 3 to 4 weeks old, after these animals had passed the government inspection. Neither of these houses mixed the glands of different kinds of animals. They both courteously and fully described their process of selection and desiccation. The Phospho-Albumen Company replied that they used the thymus gland from young lambs (young sheep) only, and described the process by which they make an extract instead of a desiccated preparation. These three American preparations, as we see, differ from each other either as to the source or method of preparation. If we could have the active agent or agents, our therapy would be more scientific and our observations more definite.

The dose of thymus preparations at present, is "enough." Small doses are best, at first, given tentatively, to determine individual reaction and tolerance,

but I have seen no bad result from very large doses. The raw or slightly cooked glands have been given in quantities of one-half ounce or more, in single or divided doses, daily or thrice weekly or less often. Of the commercial powders and tablets I have given from 5 to 90 grains daily. To get and keep good results the medication should be given persistently for long periods.

Its application is not to accidents, such as acute infections, but to affections of metabolism; and chronic diseases must receive chronic treatment.

EXOPHTHALMIC GOITER.

Thymus therapy is due, in a measure, to a butcher's happy ignorance.

Mr. David Owen,³ of Manchester, England, administered, as he thought, large doses of thyroid gland to a patient with exophthalmic goiter, and recovery ensued. As a rule, thyroid feeding injures such patients, though I have myself observed and reported one of the exceptions to this rule on record. At the instance of Dr. Hector Mackenzie, who observed that the quantity of gland substance given by Mr. Owen would require several thyroids, further inquiries were made, and it was found that the butcher had been furnishing thymus—"neck sweetbread"—instead of thyroid gland.

Mr. Owen then deliberately began the use of the thymus gland from the calf. In one of his cases which did not improve, it was found that the thymus gland furnished was from the sheep, and on the substitution of calves' thymus glands, improvement began. The good effects noted were greater or less reduction of the thyroid tumor, great reduction of the tachycardia, and control of the nervous symptoms, together with improvement of the general nutrition.

Another British observer, Mr. Todd,⁴ has published a noteworthy case, with sphygmographic tracings and pulse chart absolutely convincing. The case was one of severe exophthalmic goiter, in which rest and all of the approved drugs had been used, notwithstanding which the cardiac symptoms became steadily worse. This patient had finally recovered under the administration of fresh thymus gland from the calf. I call attention to this particular case as one which entirely meets the

criticisms of Dr. Hector Mackenzie, of London, Dr. Kinnicutt,⁶ of your city, Dr. Parker,⁷ of London, and other good observers who have used thymus gland in exophthalmic goiter without noting special benefit; while Watson Williams's⁸ patient was apparently made worse by the treatment.

Parker's patients, however, professed to feel much better for the medication, despite the lack of objective improvement. Furthermore, many competent and experienced physicians, in Europe and America—Mikulicz,⁹ Cunningham,¹⁰ Edes,¹¹ McKie,¹² Maude,¹³ Reinbach,¹⁴ and others—have had favorable results that are not to be attributed either to suggestion or to the well-known tendency of Graves' disease to spontaneous improvement or recession. I have elsewhere published my own¹⁵ good results with the use of thymus gland in the treatment of exophthalmic goiter. Its effect is especially marked upon the nervous symptoms, but Todd's case illustrates its power over the heart, and Mikulicz, Bruns¹⁶ and others have shown its influence upon goiter, both in connection with and apart from Graves' disease. Upon the proptosis its effect is perhaps least.

Recently I suspended the use of thymus gland in this disease, not because it did not give good results, but because the adrenal substance promised even better ones. I have found, however, that some cases present symptoms that can be controlled by thymus gland and not by adrenal gland, while others present symptoms that can be controlled by adrenal but not by thymus. A combination of the two has thus seemed to me better than the use of either alone; but I have not yet had a sufficient number of cases treated in this way for a long enough time to warrant reporting them or drawing conclusions. At one time I thought that adrenal produced less effect upon the goiter, more upon the heart, than thymus; but in other cases the reverse has been noted. The puzzling pathology of exophthalmic goiter gives us no help in theorizing, and empirically this adds but one more to the contradictory observations.

PHYSIOLOGIC AND PATHOLOGIC MEMORANDA.

Physiologists do not give us much help as yet as to the nature of the active principle of the thymus gland, or as to its function in the human body. Foster¹⁷ says

that from the gland a proteid-like globulin may be extracted, which seems to have some special relation to the formation of fibrin. When injected into the veins it gives rise to extensive vascular clotting. The thymus gland is rich in extractives—xanthin, hypoxanthin, leucin, lactic, succinic and other acids have been found in it. "Its chief function," he states, "seems to be associated with events taking place before birth, or in early life."

Beard¹⁸ has recently revived the hypothesis of Kölliker that the thymus gland is concerned in the production of leukocytes. His argument is founded on observations made on the smooth skate—*Raia batis*—which seemed to show that the earliest production of leukocytes was in that sac developed from the primitive branchial arch, which later on becomes the thymus gland. These cells he believes to be the parents of all the glandular structures. Cases have been reported in which the enlargement of the thymus gland has been associated with leukemia or hyperleukocytosis. These are of many kinds. In some cases tumors, genuine sarcomata are found;¹⁹ in other cases vague hyperplasias, perhaps associated with general lymphatic enlargements, as in the status lymphaticus. In acute leukemia²⁰ and Hodgkins' disease there have been found tumors of the thymus gland, some of which have been reported as sarcomata, but which later observation seems to have demonstrated to be collections of cells resembling in their nature and arrangement such a process as would be expected from a revival of the involuted thymus.

In exophthalmic goiter the thymus gland is frequently found to be enlarged at death.²¹ Owen looks upon this as a compensatory revival. It is also found to be enlarged in akromegaly and in pulmonary hypertrophic osteoarthropathy; perhaps similarly in an effort of nature (reaction) to restore by supplement or antagonism a disturbed metabolic balance.

A number of cases of epilepsy²² with mania have been reported in which the thymus gland has been found enlarged at death. These cases are supposed to indicate some toxic properties of the excessive thymus secretion, and are thus associated with thymic asthma. But the evidence is susceptible of other interpretation.

EXPERIMENTAL THYMECTOMY.

Removal of the thymus gland has been attempted by some observers, with unsatisfactory results.

The thymus gland is found to be a necessary organ in the frog, but less so in dogs.

I quote from Norton's²³ excellent summary, verified by reference to his sources.

Tarrelli²⁴ extirpated the gland from dogs, with the following results:

1. No dog died of the operation.
2. Dogs showed a great voracity, but grew less than dogs in normal condition.
3. The blood showed a diminution of red-cells and hemoglobin, but an increase of leukocytes, which kept on increasing from one to one and a half months after operation; it showed also the presence of eosinophiles.
4. Dogs showed loss of strength four months after the operation.
5. Dogs' hair did not grow as well as in unoperated dogs; it lost its brilliancy, became very rough, and fell out easily.

The author draws no conclusions as to the action of the gland from these cases.

Abelous and Billard,²⁵ working together on frogs, give the following summary of their experiments:

1. The thymus in the frog is an indispensable organ for life.
2. Its total ablation is followed by severe troubles: *a*, dynamic—weakness, paresis, paralysis; *b*, trophic, discoloration of the skin, cutaneous ulcerations; *c*, alterations in the blood—hydremia, edema, hemorrhages, changes in the corpuscles.
3. Ablation of one thymus does not induce death.
4. We believe that frogs deprived of the thymus die of a true autointoxication, as shown by the manifest toxicity of their secretions, when injected into frogs lately operated upon.
5. Subcutaneous insertion of the thymus does not prolong life materially, though it may restore the normal color of the skin.
6. Injection of a thymus extract from cattle into frogs causes an augmentation of the excito-reflex power of the spinal cord; at the same time the color of the skin

becomes markedly darker, and if discoloration has commenced, the frog takes on its natural color. The effect of these injections seems then to present a true antagonism to the troubles which follow the extirpation of the thymus.

EXPERIMENTAL EFFECTS OF THYMUS EXTRACT.

"It is Svehla,²⁶ however, who has up to the present time done the best experimental work with the thymus gland. He worked with a watery extract of human glands, as well as with glands from other animals. He states that intravenous injection of the thymal extract from man, cattle, dog, and pig, causes in dogs:

"1. A lowering of the blood-pressure, following weakness or paralysis of the vasoconstrictors.

"2. An acceleration of the pulse, due to a direct influence on the heart.

"3. In large doses it causes death of the animal, with appearance of restlessness, followed by collapse and dyspnea. Autopsies showed death in these cases to be due to suffocation."

THYMO-URIC ACID.

Minkowski,²⁷ after feeding dogs with calf thymus or the nuclein obtained therefrom, noted a new substance in the urine, which he calls urotonic acid (imidopseudouric acid), and which he believes to be an oxidation product of the nuclein base special to the gland. It may be twenty-three times greater than the ordinary uric acid in quantity.

THYMUS GLAND AND HEMOPHILIA.

A. Clark,²⁸ of London, recently reported the case of an infant in which the thymus was found absent after death, and in which there had been extravasations of blood during life. This is interesting in connection with the known property of thymus extract to produce clotting when injected into the veins, and suggests some connection of thymic failure with hemophilia, and the use of the gland as a remedy in that affection.

PHYSIOLOGIC STYPTIC.

A. E. Wright,²⁹ of Dublin, recommends for use a physiologic styptic prepared as follows:

Fresh and finely-minced thymus is extracted from twelve to twenty-four hours with ten to twenty times its

weight of a solution containing 1 per cent. of carbolic acid and 1 per cent. of sodium chlorid; and to this is added, after straining, 0.5 per cent. of crystallized calcium chlorid. It is then made faintly alkaline, shaken and mixed with the effused blood, in the proportion of about 1 to 10.

CACHEXIA STRUMIPRIVA.

Cunningham,³⁰ of New York City, in his experiments on dogs, found that the thymus extracts were as useful as thyroid extracts in combating or preventing the *cachexia strumipriva*, and as recent observations, especially those by Mendel,³⁷ seem to demonstrate that there is no iodine in thymus and that the iodine which Baumann³² thought he had found in minute quantities in large amounts of thymus substance was, in fact, due to contamination by parathyroid substance, it is evident that the good results can not be attributed, as has been done by some, to iodine.

GOITER.

The same remark applies to Reinbach's¹⁴ clinical observations. This observer relates the experience obtained in Mikulicz's clinic with the use of thymus extract in the treatment of ordinary goiters. Fifteen cases were so treated, while for comparison eight were treated with thyroid extract and two with thyroiodine. It was demonstrated that thymus extract had a distinct influence in diminishing the size of the goiters in some cases, though nearly 50 per cent. were unaffected. Adenomata and cysts were uninfluenced both by thymus and thyroid extracts. No case recovered completely, and most of them required operation, but the remedy did no harm and gave rise to no unpleasant result. This, it is remarked, contrasts favorably with the thyroid treatment, since heart-failure is not uncommon after the exhibition of the latter. On the whole the effect of thymus treatment was thought to be greater than when thyroid extract was employed.

COMPARISON AND CONTRAST OF THYROID- AND THYMUS-ACTIONS.

These experiments and experiences, showing a certain similarity between the action of thyroid and thymus substances, need to be harmonized with other observa-

tions showing dissimilarity or antagonism. Doubtless further research will show that the secretions of the ductless glands are complex; that there is a difference, physiologic and pharmacologic, between the gland-substance and the secretion; that both cell and cell-product change under diverse conditions; that, as with plants, for example, belladonna and pilocarpus, so with animal tissues, proximate principles largely antagonistic may exist side by side. This being done, we may then be able to find out just why certain substances in the two glands, or even the whole secretions, have under differing conditions opposing or supplementary functions. Cunningham, like Svehla, found that the thymus extracts depressed blood-pressure by a vasodilating influence; but according to my clinical experience, the blood-pressure is raised and vasodilation corrected by the administration of the thymus gland. Perhaps different conditions or the use of different active agents may be involved.

This much is certain, that in that group of cases to which I have called professional attention, under the name of vasomotor ataxia,³⁶ two distinct subclasses may be made; the one exhibiting greater tendency to undue relaxation of the vessels and finding its extreme type in Graves' disease; the other exhibiting a more marked tendency toward undue contraction of the vessels and finding its extreme type in Raynaud's disease. Between these two extremes exist all varieties, often with commingling of diverse tendencies toward vascular instability. Among the phenomena by which the two classes may usually be separated, the temperature-relation, that is, the reaction to heat or to cold, is prominent. Subjects of the one class complain of excessive heat sensations, undue sweating and the like, even in comparatively mild summer weather, feeling, on the other hand, relatively comfortable in winter. Those of the other class suffer from moderate cold to a degree, and with symptoms, which, in the majority of men, it would require zero weather to produce, while summer is to most of them a time of comparative enjoyment; the exception being the infrequent cases in which a lack of perspiration even in summer is a source of distress. Administration of thymus or adrenal extract to those with undue dilatation of vessels—the summer patients—and of thy-

roid extract to those with undue constriction and want of perspiration—the winter patients—is often followed by relief of symptoms. Hence I am constrained to believe in a physiologic antagonism between the thyroid and the thymus—at least so far as vascular constriction and dilatation are concerned—in the patients and under the conditions mentioned. While I have observed some gratifying recoveries following the use of thymus substance, with and without the adrenal substance, in these cases, and in urticaria and asthma, and for the correction of the neurovascular disturbances of the menopause, I have also to record many failures; whether the cause of failure lies in the theory of therapy, in the diagnosis, or in further and undiscovered idiosyncrasies of the patient I know not.

CATEGORIES OF ORGANO-THERAPY.

Thus far we have dealt with what may be termed physiologic uses of thymus extract in therapeutics. As I have elsewhere pointed out, the therapeutic uses of animal tissues and secretions fall into three categories, which may be termed, respectively:

1. Homologous or direct physiologic organotherapy; in which actual or relative deficiencies in the functions of certain organs of the patient are remedied by the administration of functional substances derived from similar organs of the lower animals. This is best illustrated by the use of digestive ferments in indigestion, and of the thyroid preparations in myxedema.

2. Physiologic organotherapy of the indirect type; in which the apparent function in the human body of a certain organic product leads to the administration of the like substance from animals for the production of a similar effect; and this, even when disease or deficiency of the given organ or secretion is not to be demonstrated or may not be suspected. The use of adrenal substance locally or internally to produce vasoconstriction is the most conspicuous example of this class.

3. Heterologous organotherapy; in which the pharmacologic properties of substances of animal origin are used for the production of effects having no reference to the physiologic uses or pathologic capabilities of the living gland in the human body. Just as strychnin or arsenic affects the animal metabolism and produces cer-

tain toxic or therapeutic results, so do substances of animal origin; and it may be that such uses will be found for all animal extracts.

EMPIRIC USES OF THYMUS GLAND SUBSTANCE.

Under this last head, perhaps, come the empiric uses of the thymus gland, to which I shall now direct your attention.

Following Mackenzie's⁵ suggestion, that the good effect of thymus gland in certain cases of exophthalmic goiter was due purely to its influence upon nutrition, Kinnicutt,⁶ and others, gave it to patients with pulmonary tuberculosis, noting during its use an increase in weight, with subsequent loss upon its withdrawal. It has been used with reported good results in rachitis and in marasmus. In one case of rheumatoid arthritis, associated with exophthalmic goiter, under my own care, the joint conditions improved, together with the general condition of the patient. I have since employed it in six cases of uncomplicated rheumatoid arthritis, with relief in one case, and with failure in the others. Macalister,³³ probably the first to use thymus gland deliberately as a therapeutic agent, found it remarkably useful in a case of pseudo-hypertrophic paralysis. Its use in chlorosis, by Blouet,³⁴ may either be nutritive or may be brought into relation with the narrowing of the aorta found alike in chlorosis and in cases of the *status lymphaticus* with enlargement of the thymus gland.

Chittenden³⁵ has shown that the lymphoid cells of the thymus gland contain a much larger proportion of phosphorus—3.5 per cent.—than is to be found in the nucleoproteid of any organ except the pancreas—4.71 per cent. This richness in an easily assimilable element, which is certainly of profound importance in the structural and functional metabolism of the higher tissues, may explain the good effect of thymus therapy in diseases of nutrition. Its good effect in exophthalmic goiter I believe to be connected with its physiologic function, probably falling under the second rather than the first of our categories; but as to this, in common with nearly all other problems relating to the thymus gland, we still await further information from careful, scientific and skilful observations, in which I trust other New York

physicians will do as good work as has been done by those of your colleagues whose names I have so frequently mentioned.

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