ciation, Professor Theodore Gill, of Washington, D. C., as Senior Vice-President, will call the meeting to order and introduce the President-elect, Professor Wolcott Gibbs, of Newport, R. I. Addresses of welcome will be made by Mayor William C. Maybury and Hon. Thomas W. Palmer, and President Gibbs will reply. Announcements by the General, Permanent and Local Secretaries will be made and after adjournment the Sections will be organized.

On the afternoon of Monday, August 9th, the Vice-Presidents of the Sections will make addresses as follows:

At half-past two o'clock. Vice-President Barus, before Section of Physics: 'Long Range Temperature and Pressure Variables in Physics.' Vice-President McGee, before Section of Anthropology: 'The Science of Humanity.' Vice-President White, before Section of Geology and Geography: 'The Pittsburg Coal Bed.'

At half-past three o'clock. Vice-President Beman, before Section of Mathematics and Astronomy: 'A Chapter in the History of Mathematics.' Vice-President Colburn, before Section of Social and Economic Science: 'Improvident Civilization.' Vice-President Howard (nominated by Council to fill vacancy caused by the death of Dr. G. Brown Goode) will give by request of the Council an address before Section of Zoology, subject to be announced.

At half-past four o'clock. Vice-President Mason, before Section of Chemistry: 'Sanitary Chemistry.' Vice-President Atkinson, before Section of Botany: 'Experimental Morphology.' Vice-President Galbraith, before Section of Mechanical Science and Engineering: 'Applied Mechanics.'

On Monday evening Dr. Theodore Gill will give a memorial address on the life and work of the late President of the Association, Professor Edward D. Cope.

The meetings of the Sections will follow on the mornings and afternoons of Tuesday, Wednesday, Thursday and Friday. It is expected that on two days of the week the Geological Society of America and the American Chemical Society will hold meetings occupying the time of Sections E and C.

The usual receptions and excursions have been planned, including a visit to Ste Claire Flats, on Saturday after the adjournment. It is expected that the members of the Association at Detroit will go in a body to Toronto to join in welcoming the members of the British Association to America. For this purpose special rates will probably be secured by steamer and train from Detroit to Toronto.

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*INTERNAL SECRETIONS, CONSIDERED FROM A CHEMICO-PHYSIOLOGICAL STANDPOINT**

In considering this subject from a chemico-physiological standpoint allow me at the outset to emphasize the fact, now well established, that the symptoms which follow the simple removal of a physiologically active gland from the body result wholly from the loss of the gland. You may recall that when attention was first drawn to the possibility of producing the typical symptoms of myxœdema in monkeys by removal of the thyroid gland there was a tendency to assume injury to the sympathetic or other nerves of the neck as an explanation of the phenomena, rather than to admit the possibility even of a general or limited disturbance of the metabolism of the body through chemical changes associated with removal of the gland. It was not until the experiments of Murray made clear the fact that the effects resulting from the removal of the thyroid in man could be overcome, in part at least, by administration of the gland-substance that scientific investigation took the proper turn and a full realization of the possible importance of the so-called ductless glands and their internal secretions began to dawn upon the mind. To-day, however, we recognize their functional activity as a necessary element for the welfare of the body. Their removal, or any impairment of their function, may produce even more disturbance of physiological equilibrium than a corresponding disarrangement of glands formerly consid-

*Read at the Fourth Triennial Congress of American Physicians and Surgeons, May 5, 1897.

ered of greater physiological value. Further, it needs to-day little argument to support the view that such power as these physiologically active glands possess is due to definite chemical compounds elaborated by the glands as products of their individual secretory or metabolic activity. As with other glands having more obvious functions, the secreting cells plainly manufacture certain specific products, but in the case of the internal secretions these products find their way into the blood and lymph, by which they are distributed throughout the body, and thus made available either in controlling or regulating the general nutrition of the economy or to serve some more specific purpose of equal importance for the welfare of the organism. This being so, it is equally probable that in the general and specific metabolism going on in all the tissues and organs of the body the various products formed and absorbed by the blood and lymph may contribute somewhat to the welfare of the body prior to their excretion. In its broadest sense, therefore, internal secretion must be looked upon as something common to all active tissues, the ordinary katabolic products of both circulating and morphotic proteids, for example, no doubt exerting some physiological action during their transit from the place of their formation to the organ which serves for their excretion. It is well, perhaps, to give full recognition to this possibility, for physiological equilibrium in the broadest sense is clearly dependent upon the harmonious action of a large number of related parts, and experiment only can determine, and perhaps then imperfectly, how far the products of one gland or tissue are essential for the well-being of the whole. We know, however, that certain organs with the products they elaborate can be dispensed with, while the removal of other organs involving no greater surgical interference is quickly followed by marked disturbances and later by death. Czerny had no difficulty in removing the stomach from dogs, the health of the animals remaining unimpaired when the œsophagus was properly joined to the intestine. Similarly, Schäfer and Moore* have recently shown that both parotids and both submaxilliary glands may be removed from the dog without any disturbance of nitrogenous metabolism, or without any apparent effect upon carbohydrate digestion. Evidently these glands do not possess any intrinsic internal secretion necessary to the life of the animal or having any important action on the metabolic processes of the body. If they do furnish an internal secretion it obviously must be one common in function to that supplied by some other organ. In the present discussion, therefore, we may advantageously limit the term 'internal secretion' simply to those specific products which, being manufactured in certain definite glands, are plainly endowed with well-defined physiological action.

Let us first consider the thyroid gland upon which more work has been done than upon any other similar structure. Dating from 1883, when Kocher and Reverdin published their well-known observations on the effects of thyroidectomy in the human subject, it has gradually become apparent that there are two distinct ways in which the effects of the operation may be manifested.† Thus, in some animals, as in most carnivora, complete removal of the thyroidal tissue is followed by a rapid development of symptoms indicating a marked irritation of the nervous and muscular systems as manifested by tetanus, epileptiform convulsions, etc., terminating in death. In other cases

*Proceed. Physiol. Soc; Journal of Physiol. Vol. 19, No. 4.

† Compare Roos: Ueber die Einwirkung der Schilddrüse auf den Stoffwechsel nebst Vorversuchen über die Art der wirksamen Substanz in derselben. Zeitschr. f. physiol. Chem. Band 21., p. 19. This paper contains numerous references.

slowly developing changes are observed corresponding to myxœdema. Hence, in some animals thyroidectomy is followed by such a marked disturbance of physiological balance that death results very quickly, while in others the development of symptoms is very slow, giving rise to chronic effects which may endure for months. Evidently, aside from the more acute and toxic effects which may immediately follow the operation, there are more gradual disturbances of metabolism which eventually lead to the complete breaking down of the animal. That the symptoms thus produced are dependent upon the withdrawal from the system of certain specific products is evident from the fact that after extirpation of the thyroidal tissue the mere feeding of thyroid glands, or the subcutaneous and intravenous injection of thyroid extracts, suffices to quickly dispel the myxoedemal swellings, the rough thickened condition of the skin, the muscular and mental apathy, etc.* With dogs the convulsions which follow extirpation of the thyroids are quickly checked by the subcutaneous injection of thyroid extracts. Experiments along these lines with extracts of dead tissue have, as you know, made it very evident that the thyroid gland forms some one or more specific substances, the absence of which from the body sooner or later renders life impossible. Where, however, the animal, as a dog, is provided with accessory thyroids the entire thyroid gland may be removed without death resulting, providing one of the parathyroids is left, but if both parathyroids are excised then 40 per cent. of the thyroidal tissue proper must be left in order to have the dog live.† Evidently, the thyroids and accessory thyroids have more or less of a common function, the one being able to fulfil the purpose of the other to a certain degree; a fact which in itself may be taken as evidence of the importance of thyroidal tissue and the care exercised by nature in preventing its complete suppression.

The very nature of the physiological results which follow the removal or accompany the atrophy of the thyroidal tissue suggests the formation of one or more toxic substances to which the well marked symptoms are due; substances which are either not formed in the presence of thyroidal tissue or else being formed are either neutralized (physiologically) or decomposed and rendered inert by substances furnished by the thyroid gland. Such a view obviously implies a difference in the character and possibly in the extent of the metabolic changes going on in the body, and we may, therefore, advantageously consider the character of our knowledge upon this subject. A careful study of the literature shows quite clearly that certain definite statements are justified. Thus, Leichtenstern and Wendelstadt* found by feeding thyroid glands to healthy obese individuals that a marked loss of body-weight resulted. Roos,† experimenting with normal dogs, observed that in feeding the gland substance for several days there was a marked increase in the excretion of nitrogen through the urine, also of sodium chloride and of phosphoric acid (P_2O_5). On dogs with the thyroids removed, this action was still more marked, so far as the excretion of nitrogen and chlorine was concerned, also in the loss of body-weight and in the excretion of water, but the excretion of phosphorus fell behind the normal. Further, in an ex-

* See Kent: Thyroid extract after Thyroidectomy. Proceed. Physiol. Soc; Journal of Physiol. Vol. 15. Also Meltzer: Ueber Myxödem. Centralbl. f. Physiol. 1894, p. 698.

† Edmunds: Observations on the Thyroid and Parathyroid of the Dog. Journal of Physiol. Vol. 22. Proceed. Physiol. Soc. June 27, 1896.

* Ueber Myxœdem und Entfettungskuren mit Schilddrüsenfütterung. Deutsch. med. Wochenschr. 1894. No. 50.

† Loc. cit.

periment with a goitre-patient, otherwise healthy, Roos observed on feeding thyroid glands a similar tendency towards increased excretion of nitrogen and chlorine with a marked increase in the output of phosphoric acid. Mendel, Napier, Ord and others, making observations on myxoedema patients, likewise noted that the use of thyroid preparations by subcutaneous injection, by glycerin extracts, etc., as a rule, not only led to a betterment of the symptoms, but gave rise to a marked diuresis, loss of body-weight and increased excretion of nitrogen or urea. Denning,* likewise, found that while different individuals reacted somewhat differently under thyroid feeding, yet there was a general tendency toward increased excretion of nitrogen as well as a loss of body-weight. It was also noted that the excretion of nitrogen and urea was not always parallel. Occasionally albumin and sugar appeared in the urine. In one case the volume of urine excreted rose at once 200 cc. per day, the pulse rate increased 22 per cent., while the nitrogen excreted rose 15 per. cent during the feeding period. Similarly, in Basedow's disease, Scholz† observed under the influence of thyroid feeding in a patient 29 years old diuresis, increased excretion of nitrogen and sodium chloride with a marked decrease in the excretion of phosphoric acid. Magnus Levy‡ likewise records that a healthy individual taking thyroid tablets for 19 days lost 7 pounds body-weight with some increase in O_2 and Co_2 exchange. In three cases of Basedow's disease, on the other hand, oxygen consumed and carbonic acid excreted were greatly in excess of the normal. Fritz Voit,* by carefully conducted experiments on healthy dogs, found that the feeding of fresh thyroid glands produced a marked increase in the output of carbonic acid as well as of nitrogen. Michaelson† found after extirpation of the thyroid in hungry cats the Co_2 excretion increased, while J. L. Smith‡ has observed that when thyroidectomy is performed on cats there is a marked disturbance of the heat-regulating mechanism.

From these and other observations that cannot be recorded here it is very plain that the administration of thyroid gland and thyroid extracts to normal individuals, and especially to thyroidectomized animals and individuals in whom the thyroid glands are diseased, produces a very noticeable effect upon the metabolism of the body, leading to a marked loss of body-weight, an increased excretion of water, nitrogen and carbonic acid, and also of sodium chloride. This great diminution of body-weight is by no means due wholly to loss of water nor to removal of fat, for if a healthy individual is fed upon a diet rich in fats and carbohydrates the well-known proteid-sparing power of the latter foods is not able to keep down the loss of nitrogen when thyroids are administered. Proteid material is still broken down in increased quantity, and not from any individuality of the person experimented upon, but plainly under the ex-

* Ueber das Verhalten des Stoffwechsels bei der Schilddrüsentherapie. Münchener med. Wochenschr. 1895. No. 17. Also No. 20.

† Ueber den Einfluss der Schilddrüsenbehandlung auf den Stoffwechsel des Menschen insbesondere bei Morbus Basedowii. Centralbl f. innere Med. Band 16, p. 1041 and p. 1069.

‡ Ueber den respiratorischen Gaswechsel unter dem Einfluss der Thyreoidea, sowie unter verschiedenen pathologischen Zuständen. Berliner klin. Wochenschr. 1895, p. 650. See also Richter: Zur Frage des Eiweisszerfalles nach Schilddrüsenfütterung. Centralbl. f. Physiol. Band 10, p. 49. Also Ducceschi: Beitrag zur Erforschung der Stoffwechselvorgänge bei thyroidectomirten Thieren. Ibid. Band 10, p. 217.

*Stoffwechseluntersuchungen am Hund mit frischer Schilddrüse und Jodothyrin. Zeitschr. f. Biol. Band 35, p. 116.

† Jahresbericht f. Thierchemie. Band 19, p. 335.

‡ On some effects of Thyroidectomy in animals. Journal of Physiol. vol. 16, p. 378.

citing influence of the thyroid.* The gland substance evidently causes an increased decomposition of the tissue proteids, thus showing a certain resemblance to the action of phosphorus on the organism (Roos). At the same time the loss of body-weight under thyroid feeding is far greater than can be accounted for by the increased proteid decomposition, from which, in conjunction with the increased gaseous exchange, we must infer an increased breaking down of fatty tissue in accord with the prevalent idea that thyroids tend to reduce obesity. This, furthermore, is in harmony with the well-known fact that increase in proteid metabolism is almost invariably associated with increase in the metabolism of non-nitrogenous matter.

The significance to be attached to this increase in proteid metabolism, however, is, I think, something more than a mere quantitative one. The very fact that there are quantitative changes renders it quite probable that there are also qualitative changes, and that the presence or absence of the thyroid gland or its equivalent from the body may modify the *line* of metabolism. Upon this point, however, we know very little; we simply infer. Still there are some facts in connection with the proteids of the blood which are worthy of a moment's consideration. Thus, it has been shown by comparison of the proteids of normal dog's blood with those present in the blood after extirpation of the thyroids that in the period preceding the convulsions the percentage amount of serum-albumin is increased and the globulins decreased. In the second period, on the other hand, when the cramps or convulsions appear up to the end, there is a progressive increase in the amount of globulin and a decrease of serum-albumin as well as of the total proteid. Hence, there is at first an increase and then a decrease of the albumin quotient. From this it would appear that in the first stages there is an abatement of the metabolism of the tissues, followed by an increase, and that possibly in the incomplete breaking-down of the proteid material intermediate toxic products appear which are the cause of the cachexia.* Further, according to Formánek and Haskovec,† in the thyreopriva cachexia, resulting from the extirpation of the thyroids in dogs, the number of red blood corpuscles is systematically diminished, while the leucocytes are increased, and the dry residue of the blood as well as the iron and hæmoglobin are diminished. In connection with the diminution of hæmoglobin there is an acceleration of respiration and of the pulse, which, however, in the terminal stages of the cachexia diminishes. The iron liberated by the decomposition of the red blood corpuscles is deposited in the organs of the body, especially in the spleen and lymph glands. If the blood is taken for examination during a convulsive seizure, on the other hand, it shows a reversal of the above conditions; it is thicker, contains more solid matter, as well as iron and hæmoglobin. If extract of the thyroid is injected into the operated animal there is an immediate increase in the number of red corpuscles and a betterment of the animal's condition. Hence, the thyroid is evidently concerned in hæmatosis, and it is quite possible that the decomposition of the blood which takes place induces certain alterations in the formation of the end-products of metabolism, so that poisons result which give rise to intoxication of the organism. Just here it may be

* Bleibtreu und Wendelstadt. Stoffwechselversuch bei Schilddrüsenfütterung. Deutsche med. Wochenschr. 1895, p. 348.

* Beitrag zur Lehre über die Function der Schilddrüse, Jahresbericht f. Thierchemie, 1895, p. 375.

† Ducceschi: Ueber die Bluteiweissstoffe des Hundes im Verhältniss mit den Folgen der Schilddrüsenexstirpation. Centralbl. f. Physiol. Band 9, p. 359.

mentioned that some recent observations on the feeding of thyroids in insanity tend to show that the percentage of the small mononuclear cells or lymphocytes of the blood are increased while the multinuclear neutrophiles are correspondingly diminished under the action of the drug, thus suggesting that the gland-tissue or its active principle has a direct stimulating influence upon those tissues of the body directly concerned in the production of the lymphocytes, viz, the lymphatic or adenoid tissues.*

In addition to these changes, emphasis must be laid upon the apparent connection between the thyroid gland and phosphoric acid metabolism. Thus, the increased excretion of P_2O_5 after feeding thyroids to normal animals, and the great decrease in the case of animals with the thyroids removed, is naturally suggestive. The facts may be explained in two ways: either the metabolism of phosphoric acid and its excretion are retarded in the absence of the gland, so that there is a retention of P_2O_5 in the body, or else the organism can assimilate sufficient phosphoric acid only in the presence of the substance or substances furnished by the thyroid gland (Roos). It has been suggested, as you know, that the activity of the thyroid gland is a toxic one, but that this action is normally paralyzed by some one or more products of its own metabolism. The view that in the absence of the thyroid gland not enough P_2O_5 can be assimilated for the wants of the body finds a certain degree of confirmation in some of the symptoms noticeable in cretinism and myxoedema; viz, the retardation in bone-development and the slow calcification in cretinism. On the other hand, the tendency toward tetanus might perhaps be explained on the ground of an acute P_2O_5 retention in the central nervous system similar to that of uræmia; or, equally plausible, as due to a marked deficiency of P_2O_5 in this tissue. Thus, in Basedow's disease the observations of Kocher that administration of sodium phosphate leads to a marked betterment of all the symptoms are directly pertinent.

Further, we must not overlook the fact clearly shown by Halliburton,* in connection with Horsley, that after thyroidectomy there is a distinct tendency toward an increase in the percentage of mucus in the tissues of the body, especially marked in the connective tissues and salivary glands. While this increase is not as great as at one time thought, it is still distinctly recognizable and affords additional evidence that the thyroid plays some important part in the katabolic processes of the body, and that when it is removed or diseased the normal chain or rhythm of metabolism is broken. As to the chemical nature of the products which are directly responsible for the results attending thyroidectomy or associated with a morbid condition of the thyroid we have no direct knowledge, and as to their physiological character we can only infer from the nature of the symptoms which result. It is to be presumed that the toxic products are formed not in the thyroid, but in the tissues of the body and as a result of perverted metabolism due to atrophy or alterations of the thyroid gland. The latter evidently furnishes something which either directly neutralizes toxic products common to the body, or far more probably prevents their formation through an influence upon the line of metabolism, or to give due weight to all the views which have been advanced, both suggestions may be correct.

What now is the chemical and physiological character of the protective products which thyroidal tissue evidently manufactures? To this question there are many conflicting answers; still out of the chaotic mass of material available I think it is pos-

* Perry: Some studies of the blood in Thyroid feeding in Insanity. *Medical Record*, August, 1896.

*See Halliburton's Handbook of Chemical Physiol., p. 505.

sible to draw certain definite conclusions. In the first place it must be remembered that the epithelial cells of the thyroid gland apparently manufacture a so-called colloid secretion which evidently finds its way into the blood through the lymph, presumably carrying with it the active principles. This secretion obviously cannot be collected for study, but such active principles as it contains may be sought for in the gland itself, since we have every reason to believe in their ready solubility. By histological methods applied to sections of the thyroid it has been shown that the colloid matter gives the general proteid reactions, that it is very soluble in dilute alkaline fluids and readily dissolved by gastric digestion.* Our knowledge of the chemical composition of the thyroid gland, and hence presumably of the colloid secretion, is due mainly to the work of Bubnow,† Gourlay,‡ Notkin,§ Moscatelli,|| Fränkel,¶ and especially Baumann and Roos,** and Hutchinson.†† To briefly summarize the present state of our knowledge, ignoring minor points of difference, I think it is quite clear that the thyroid gland is especially characterized by the presence of a compound proteid of peculiar constitution, and that this substance which Hutchinson calls 'colloid matter' is the active constituent of the gland. There is also present another proteid, a nucleo-albumin, in small amount, which Hutchinson considers as probably contained in the cells of the acini. In addition there are certain extractives to be found, viz., xanthin, hypoxanthin, inosite,* volatile fatty acids, paralactic acid, succinic acid and calcium oxalate; bodies, however, of no special physiological significance.

The chief interest centers around the above mentioned proteid material, which is plainly of a peculiar kind, since it tends to hold a certain amount of iodine in combination and yields on decomposition a peculiar non-proteid substance carrying with it most, if not all, of the iodine and endowed with marked physiological action. This latter substance, to which Baumann has given the name of thyroiodin, later changed to iodothyrin, is especially characterized, chemically, by its great resistance to ordinary decomposing agents. Digestion of the thyroid gland with active gastric juice yields the iodothyrin as an insoluble residue, but still active. The gland can even be boiled an entire day with ten per cent. sulphuric acid without loss of the active principle, the latter separating from the cooled fluid as a fine flocculent precipitate almost wholly insoluble in cold water and acid, soluble in hot alcohol and readily soluble in dilute alkalies. When purified by repeated precipitation, re-solution, etc., the body may contain as much as ten per cent. of iodine. In the gland, according to Baumann, iodothyrin exists in great part combined with albumin and in smaller amount with globulin, and these compounds are likewise physiologically active,

*Langendorff; Beitrag zur Kenntniss der Schilddrüse. Du Bois-Reymonds Archiv f. Physiol., 1889, Supplementheft, p. 219.

†Beitrag zur d. Untersuchung der chemischen Bestandtheile der Schilddrüse des Menschen und des Rindes. Zeitschr. f. Physiol. Chem., Band 8, p. I.

‡The Proteids of the Thyroid and the Spleen. Journal of Physiol., Vol. 16, p. 23.

§Zur Schilddrüsen-Physiologie. Virchows Archiv. Band 114. Supplementheft, p. 221.

||Beiträge zur Kenntniss der Milchsäure in der Thymus und Thyreoidea. Zeitschr. f. physiol. chem. Band 12, p. 416.

¶Thyreoantitoxin, der physiologisch wirksame Bestandtheile der Thyreoidea. Wiener klin. Wochenschr., 1895, No. 48.

**Ueber das normale Vorkommen des Jods im Thierkörper. Zeitschr. f. physiol. Chem. Band 21, p. 319 and 481. Band 22, p. 1.

††The Chemistry of the Thyroid Gland and the nature of its active constituent. Journal of Physiol. Vol. 20. p. 474.

*Tambach. Pharmaceutische Centralhalle, March, 1896.

although less so than the iodothyrin itself. The iodothyrin of Baumann is thus a non-proteid cleavage product of a more complex body, naturally present in the gland and characterized by containing both iodine and phosphorus (0.5 per cent.). Aqueous and glycerin extracts of the gland contain iodothyrin or the mother-substance, although they do not take up all of the substance. Extraction of the gland with 0.75 per cent. sodium chloride solution, frequently repeated, removes all of the iodine-containing substance, and the residual tissue has little or no effect upon goitre.*

That iodothyrin possesses all the peculiarities associated with thyroid-therapy is, I think, pretty thoroughly established. The experiments of Roos† upon animals, and the clinical observations of Leichtenstern and Ewald, have clearly demonstrated the physiological power of the substance. Its action on goitre,‡ as tested in over a hundred cases, is very noticeable. In the parenchymatous form a few day's treatment suffices to greatly reduce the size of the swelling. Normal dogs in nitrogenous equilibrium, treated with iodothyrin, suffer a marked loss of body-weight, an increased excretion of nitrogen, NaCl and P_2O_5, while diuresis is equally marked (Roos). Further, comparative experiments by Fritz Voit,§ most carefully conducted on dogs in nitrogenous equilibrium, with fresh thyroid and iodothyrin show that the latter has practically the same action as the former in increasing the decomposition of fat and in stimulating the metabolism of proteid matter. In myxœdema the physiological action of iodothyrin is equally pronounced. Thus, in one case,* a 16-year-old patient received for 6 days 2 grams of iodothyrin (= 0.6 milligram iodine) daily. In the fore-period of 3 days she received 18.02 grams of nitrogen and excreted 17.88 grams. In the iodothyrin period she ingested 16.2 grams of nitrogen and excreted 20.0 grams, while in the 3 days after-period she consumed 15.65 grams of nitrogen and ingested 21.59 grams. In 10 days the body-weight fell 4 pounds. In the treatment of obesity iodothyrin has likewise been effective.† It has also been clearly established by experiments on dogs that iodothyrin will cut short the various symptoms produced by thyroidectomy, noticeably the convulsions.‡ As Baumann and Goldmann§ have shown, dogs with thyroids removed do not manifest symptoms of tetanic convulsions so long as iodothyrin is given regularly each day in doses ranging from 2 to 6 grams. Further, in such cases the withdrawal of the iodothyrin, or a marked reduction in the amount administered, is generally followed by an appearance of the convulsions. The dosage required to remove or overcome the tetanus of a dog suffering from thyroidectomy is greater the more vigorous the symptoms and the longer the administration has been delayed after the appearance of symptoms.

* Roos: Zur Frage nach der Anzahl der Wirksamen Substanzen in der Schilddrüse. Münchener med. Wochenschr., 1896, p. 1157.

† Ueber die Wirkung des Thyrojodins. Zeitschr. f. physiol. Chem. Band 22, p. 18.

‡ See Ewald und Bruns: Verhandlungen des Congresses für innere Medicin, 1896, p. 101.

§ Stoffwechseluntersuchungen am Hund mit frischer Schilddrüse und Jodothyrin. Zeitschr. f. Biol. Band 35, p. 116.

* Treupel: Stoffwechseluntersuchung bei einem mit Jodothyrin (Thyrojodin) behandelten Falle von Myxoedem und Mittheilung einiger Thierversuche mit Jodothyrin (Thyrojodin). Münchener med. Wochenschr., XLIII. 38, p. 885. See also Notkin, Virchows Archiv. Band 144, Supplementheft.

† See Grawitz: Beitrag zur Wirkung des Thyrojodin auf den Stoffwechsel bei Fettsucht. Münchener med. Wochenschr., 1896, No. 14. Also Henning Ibid., 1896, No 19.

‡ Hoffmeister: Deutsch. med. Wochenschr., 1896, No. 22. Hildebrandt; Berliner Klin. Wochenschr. 1896, No. 37.

§ Ist das Jodothyrin (Thyrojodin) der lebenswichtige Bestandtheil der Schilddrüse? Münchener med. Wochenschr., 1896, p. 1153.

The negative results obtained by Gottlieb* have been recently shown to be due to the employment of a poor preparation.

Does the physiological action of the thyroid gland reside wholly in this so-called iodothyrin or its antecedent? In attempting to answer this question we must give a moment's attention to Fränkel's so-called thyreoantitoxin.† This, as you may remember, is a crystalline body of neutral reaction obtained from the proteid-free extracts of the thyroid gland. It is soluble in water and alcohol, but precipitable by ether and acetone, and from its composition it has been suggested that it is a guanidin derivative. Fränkel ascribed to this substance the physiological activity of the thyroid gland, since he obtained a suspension of convulsions with thyroidectomized cats on injecting this body. Further, Drechsel‡ has made a preliminary communication to the effect that the proteid-free extract of the thyroid from pigs contains two crystalline substances in small amount, which when fed to thyroidectomized animals appear somewhat active, although not strongly so. Drechsel therefore suggests that possibly there may be three active substances present in the thyroid, viz, two bases, one identical with Fränkel's antitoxin, and Baumann's iodothyrin. He would thus ascribe to the thyroid several associated functions and corresponding to each a distinct chemical substance. Theoretically, of course, this is quite plausible, but Drechsel's compounds have not been further heard from and there are many recent observers who fail to find any physiological action whatever with the proteid-free extract from the gland.§ Moreover, careful comparative study of the action of thyreoantitoxin and iodothyrin in a myxoedema patient showed that while the former was entirely without beneficial action the latter produced all the results characteristic of thyroid feeding.* Further, Roos,† by experiment on a normal dog in nitrogenous equilibrium, found that thyreoantitoxin was wholly without influence on metabolism, while iodothyrin given to the same animal under like conditions caused at once a marked increase in the output of nitrogen, NaCl and P_2O_5. In other words, thyreoantitoxin shows with certainty none of the properties of the thyroid gland, while iodothyrin is apparently the physiological equivalent of the gland. Indeed, in its action on goitre iodothyrin is more effective than the gland itself, since when the gland is taken it must first undergo digestion to liberate the iodothyrin and some may be lost by putrefactive changes in the intestine.

What now is the significance of the iodine contained in the so-called iodothyrin? Iodine is not a common constituent of the animal body, and its discovery by Baumann in the thyroid gland toward the end of 1895 was the first intimation of its presence in the human organism. So far as known, it is not normally present to any extent in other tissues.‡ Traces, however, are found in the thymus of the calf (Baumann).§ Barrell has likewise reported the presence of traces in the spleen, adrenals and the ovaries of pigs and cows. The amount, however, is very small as compared with that found in the thyroid. Calling the amount of iodine in 1 gram of fresh thyroid as 1, the spleen contains $\frac{1}{20}$, the adrenals $\frac{1}{130}$, and the ovaries

* Deutsch. med. Wochenschr., 1896, No. 15.

† Wiener klin. Wochenschr., 1895, No. 48.

‡ Die Wirksame Substanz der Schilddrüse, Vorläufige Notiz. Centralbl f. Physiol. Band 9, p. 705.

§ See Hutchinson: The chemistry of the Thyroid Gland and the nature of its active constituent. Journal of Physiol., Vol. 20, p. 491.

* Magnus Levy: Deutsche med. Wochenschr., 1896, No. 31.

† Münchener med. Wochenschr. 1896. No. 47.

‡ Drechsel has reported finding a distinct trace of iodine in the hair of a syphilitic patient treated for a long time with postasium iodide. Centralbl. f. Physiol. Band 9, p. 704.

§ Vorkommen von Jod in den Ovarien. Chemisches Centralblatt, 1897. Band 1, p. 608.

$\frac{1}{62}$–$\frac{1}{65}$ per gram of fresh tissue. Iodine has likewise been detected in the human hypophesis.*

In human thyroids, on the other hand, as well as in the thyroids of sheep, oxen and pigs, iodine is most generally present in quite appreciable amount, and pure iodothyrin may contain as much as 10 per cent. of the element. In iodothyrin the iodine is in close combination with the rest of the molecule and is not easily split off even by the action of alkalies. It is noticeable that the thyroids of sheep (and of other animals) vary greatly in their content of iodine. Thus in sheep coming from Freiburg 1 gram of dry thyroid gland contained on an average 0.9–1.3 milligrams of iodine, while the thyroids from Paris sheep contained 1.15–1.2 milligrams of iodine per gram of dry gland, and those from Elberfeld 1.5–5. milligrams per gram of dry tissue. As judged by the rate and intensity of physiological action 0.25–0.3 milligram of iodine in the form of iodothyrin is equal to 1 gram of fresh thyroid gland. Further, according to Baumann, doses of 1 milligram of iodothyrin which contain only $\frac{1}{10}$ milligam of iodine will produce a decided effect upon goitre after 3–4 applications, thus clearly indicating that it is not the iodine *per se* that is effective, but rather the iodine compound.

The content of iodine in human thyroids is likewise variable, the determining factor being apparently the locality in which the individual lived. Thus, in 26 adults dying from various causes in Freiburg the average amount of iodine in the thyroid was 0.33 milligram per gram of dry tissue, while in Hamburg the average from 30 adults was 0.83 milligram per gram of dry tissue. In Berlin, average of 11 adults, 1 gram of dry thyroid contained 0.9 milligram of iodine. It should be noted, however, that in the Freiburg cases the average weight of the gland was 8.2 grams with a total content of 2.5 milligrams of iodine. In Berlin, on the other hand, the average weight of the dry gland was 7.4 grams with a total content of 6.6 milligrams of iodine per gland, and in Hamburg the dried gland weighed only 4.6 grams, with 3.83 milligrams of iodine.

Recently Weiss* has reported the results from fifty analyses of thyroids of adults and children in Silesia, the average weight of the dried gland being 7.2 grams and with an average content of 4.04 milligrams of iodine.

From a large number of observations among children and adults in different localities in Germany, Baumann concludes that in Freiburg, where goitre is endemic, the weight of the thyroid is the largest and its content of iodine the lowest, while in Hamburg and Berlin, where goitre is not endemic, the reverse holds good. As a rule, in cases of goitre only minimal and almost always relatively small amounts of iodine are to be found, from which Baumann draws the conclusion that between the iodine-content of the thyroid and the occurrence of goitre there is a certain definite relationship.

I understand, however, that additional results, not yet published, tend to show that in some cases of goitre the content of iodine is far beyond the normal, thus implying the existence of two abnormal conditions: one in which the iodine-content is below, and another in which it is far above the normal. In old age the content of iodine frequently falls to a minimum, apparently in harmony with the degeneration of the gland. The largest amount of iodine is found between the ages of twenty-five

*Schnitzler und K. Ewald; Ueber das Vorkommen des Thyrojodins im menschlichen Körper. Wiener klin. Wochenschr., 1896, p. 657.

*Ueber den Jodgehalt von Schilddrüsen in Schlesien Chemisches Central-Blatt, 1897. Band 1, p. 298.

and fifty-five.* Many circumstances, however, combine to modify the content of iodine in the thyroids, especially the proximity to the sea-shore with the greater abundance of sea food, etc., and this fact, coupled with the well-known circumstance that in the thyroids of some children iodine is wholly wanting (Baumann), and this without any apparent effect upon the activity of the gland, renders one somewhat skeptical as to the real virtue of the iodine. Blum,† however, states that artificial compounds of iodine, with various forms of proteid matter, exert a beneficial influence upon parenchymatous goitre as well as upon the tetanus and myxoedema induced in dogs by thyroidectomy. The iodine in iodothyrin is certainly not active as iodine; the amount is too small, and it may, perhaps, be questioned if the amount of iodine in the thyroid gland can be taken as a measure of the amount of active substance present. In this connection it may be mentioned that animals with the thyroids removed have no power of retaining the iodothyrin administered by mouth or subcutaneously, the iodine compound appearing in the urine either unaltered or in some modified form (organic).‡

To summarize, the thyroid gland manufactures *one* specific substance of marked physiological power—the so-called colloid of Hutchinson—a body which, though containing phosphorus, is not a nucleo-proteid; neither is it allied to mucin. It is peculiar in that it contains iodine. This body when acted upon by gastric juice or by boiling acids is split into a proteid and a non-proteid part, the latter containing all of the phosphorus and the larger proportion of the iodine of the original colloid. According to Hutchinson both parts of the colloid are physiologically active, but the non-proteid part, the iodothyrin of Baumann, is unquestionably far more active than the proteid part of the original molecule. This substance is apparently the physiological equivalent of the thyroid gland. Lastly, our history would be incomplete without some reference to the theories of Notkin.* This reference, however, may be a brief one, since the theories though ingenious are now known to rest upon a false foundation and have no present value.

Concerning the other internal secretions of the body I have little to say, partly owing to lack of time and partly because there is very little definite chemico-physiological knowledge at our disposal. Our knowledge has not as yet advanced sufficiently to admit of making dogmatic statements regarding the exact chemical nature of the active principles present in the adrenals, testacles, ovaries, pancreas, pituitary body, etc., or of the exact action of extracts of these glands upon the metabolic phenomena of the body. Allow me to say, however, in reference to the adrenals that there is some evidence of the existence of two distinct physiologically active substances, one insoluble in 90 per cent. alcohol, possibly the sphygmogenin of Fränkel, which increases blood-pressure while the other, which is readily soluble in alcohol, causes paralysis of the heart and muscles and death by suffocation.† In this connection it will be

*See Baumann: Ueber das Thyrojodin. Münchener med. Wochenschr., 1896, No. 14.

†Ueber Halogeneiweissderivate und ihr physiologisches Verhalten. Münchener med. Wochenschr., 49, 1099.

‡Baumann und Goldmann, Loc. cit. See also H. und M. Frenkel. Jod im Harn nach Einnahme von Thyreodintabletten. Berliner klin. Wochenschr., xxxiii, 37, p. 827.

* Zur Schilddrüsen-Physiologie. Virchows Archiv, Band 144. Supplementheft, p. 224. This paper contains a very full bibliography. Notkin's theories are well combated by Hutchinson, Journal of Physiol., Vol. 20, p. 490.

†See S. Fränkel: Beiträge zur Physiologie und physiologischen Chemie der Nebenniere. Centralbl. f. Physiol. Band 10, p. 486. Du Bois: Note prélimi-

remembered that Oliver and Schäfer* have shown that the active principle (or principles) is non-volatile and that its activity is not destroyed by mineral acids or gastric digestion, while alkalies gradually diminish it. According to Marino-Zuco,† the toxic action is due to the presence of neurin glycerophosphate. There are also some grounds for believing a brenzcatechin-like body to be present,‡ which may exert some physiological action. Lastly, in extracts of the testis a peculiar nitrogenous body has been detected, free from oxygen, known as spermin and which is claimed by Poehl§ to have a marked influence upon metabolism and to act as a true physiological stimulus. Further discussion of these points at the present time, however, would have little value.

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naire sur l'action des extraits de capsules surrénales. C. R. Soc. de Biol., 1896, p. 14.

* The physiological effects of extracts of the suprarenal capsules. Journal of Physiol., Vol. 18, p. 370. See also B. Moore: On the Chemical Nature of the physiologically active substance occurring in the suprarenal gland. Ibid., Vol. 17. Proc. Physiol. Soc., March, 1895.

† Archiv. d. Biol. Ital., Tome 10, p. 325.

‡ Brunner: Chem. Centralblatt., 1892, I., p. 758. Mühlmann: Deutsche Med. Wochenschr., 1896, No. 26.

§ Compt. rendu. Tome 115, p. 129. Zeitschr. f. Klin. Med. Band 26, p. 133. Centralbl. f. d. Med. Wissensch., 1892, p. 950. See also Bubis: Sperminum Poehl in chemischer, physiologischer und therapeutischer Beziehung. Ibid., 1894, p. 703.

A CASE OF PRIMITIVE SURGERY.

DURING the first period of my residence among Zuñi Indians, in the autumn of 1890, I was called in to assist two medicine men or priests in the performance of a peculiarly interesting surgical operation.

A man belonging to the clan into which I had been adopted had for several months been suffering from the effects of either a contusion or a strain of the right foot, caused by a throw from his horse. This had at first given little trouble, then had appeared as an ordinary stone-bruise on the right side of the foot just below the instep. The inflammation had, however, extended until the whole foot and the lower part of the leg had become excessively swollen, so much so as to cause the skin to glisten from stretching, save at a point over and around the original injury, at which point a malignant and putrid sore had developed, the odor of which was extremely offensive, and both the foot and the leg were now of livid, purplish-red hue in places, suggestive of actual decay. As a layman in medicine I should have said that the case was now one of advanced mortification, and from the general condition of the patient I should have inferred that blood poisoning was likely soon to ensue.

I gathered from the conversation of the two old surgeons who had been called in, and who had in return requested my attendance in order that I might give 'ease medicine' and 'add with (my) breath strength and endurance to (my) clan-brother,' that it was these appearances, this apparently '*decaying* condition' of the man's extremity, that had determined them to perform the operation.

When I entered the room the patient was lying on the floor and, although in extreme agony, turned his face toward me expectantly and with a smile, uttering the customary words of welcome. His head was pillowed in the lap of his little old white-haired mother, who was gently stroking his forehead and talking to him in the endearing phrases of mothers to little children. At his side was a small bowl containing a clear but bright red liquid (made, I afterwards learned, from an infusion of willow-root bark) in which half floated, half stood, a cane sucking-tube about six inches long. The old surgeons were removing certain