

## THE ISOLATION IN CRYSTALLINE FORM OF THE COMPOUND CONTAINING IODIN, WHICH OCCURS IN THE THYROID

ITS CHEMICAL NATURE AND PHYSIOLOGIC ACTIVITY \*

E. C. KENDALL, PH.D.  
ROCHESTER, MINN.

During the past twenty years, investigation has firmly established, among other things, the following two facts: (1) The thyroid contains some substance capable of producing marked physiologic effects, and (2) iodin is a constant constituent of normal and pathologic glands. These two facts are emphasized because most of the controversies concerning the thyroid have arisen from attempts to explain the relation between the physiologic activity and the presence of iodin.

It is obvious that no final conclusions could be arrived at until either some substance possessing physiologic activity had been isolated in pure form and shown to be a normal constituent of the gland, or until the compound containing iodin had been isolated in pure form and its physiologic activity determined.

Last December <sup>1</sup> reported the separation from the thyroid of a preparation containing 60 per cent. of iodin. The present paper is a summary of the results thus far obtained. In brief, the compound containing iodin, the presence of which, as a normal constituent of the thyroid, was foretold by Baumann<sup>2</sup> nineteen years ago, has been isolated in pure crystalline form, and further, it has been shown that this compound is the substance in the thyroid which is responsible for the physiologic activity of the gland.<sup>3</sup>

Previous investigation has shown that the compound containing iodin is firmly held as a constituent of the thyroid proteins. Hence separation of this compound must be preceded by a breaking down of the proteins into the simpler constituents of which they are composed. Baumann attempted this hydrolysis, using 10 per cent. sulphuric acid, but no satisfactory cleavage of the molecule resulted. The hydrolysis which has been successful was accomplished with sodium hydroxid in alcohol as a medium for carrying out the process.

A large number of compounds are obtained by this splitting up of the protein, but they are separated into two groups by the addition of acid. Those compounds insoluble in acid are designated Group A, and those soluble Group B.

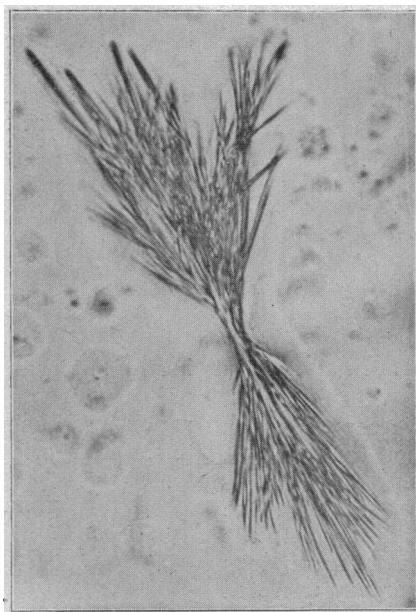
The total iodin in the gland is found to be divided almost equally between the two groups. By further hydrolysis of the A group the compound containing iodin has been separated in pure crystalline form. Its exact formula cannot now be stated, but it appears to be di-iodo-di-hydroxy-indol. It crystallizes in microscopic needles that melt around 220 C. It is very insoluble in alcohol, ether, water, acids and sodium carbonate. Dilute hydrochloric acid dissolves 1 part in about 200,000. It is readily soluble in dilute alkali and ammonia.

No definite substance possessing physiologic activity has been isolated from the B group, but it is known to be a complex mixture containing amino-acids. The iodin in B is in organic combination, but the nucleus to which it is attached is unknown.

The thyroid having been separated into several different constituents, it seemed desirable to test each one for its possible physiologic activity. It was found that the typical effects of administration of desiccated thyroid—a rapid increase in pulse rate and vigor, increase in metabolism with loss of weight, and increase in nervous irritability—are all produced by the A constituents.

The next step showed that in A, containing about 5 per cent. of iodin, the effects produced are directly proportional to the amount of iodin present. And finally, in the purification of A and the separation of the iodin compound in crystalline form, the same typical effects were produced through all the various stages of purity, up to and including the crystalline compound containing 60 per cent. of iodin.

In testing B for physiologic activity, it was found that no apparent effects are produced when B is given experimentally to a normal animal or human being, but that a considerable degree of activity is manifest when B is given to patients suffering from cretinism, myxedema and certain conditions of the



Crystals of the iodine-containing compound which occurs in the thyroid.

skin. However, no toxic effects have been produced by the administration of B, even in large amount.

This nontoxic effect of B is in strong contrast to the action of A. Although both A and B contain iodin, it has been shown that the toxicity of A is in direct proportion to its iodin content, but B iodin given in equal amount produces no apparent effect.

As previous investigators have pointed out, it is not iodin per se that is necessary. This work shows that it is the iodized indol that produces the physiologic activity. The actual amount of the crystalline iodin compound necessary to produce marked effect is exceedingly small. A total of 11 mg. (one-sixth grain), given in divided doses during a period of fourteen days to a cretin weighing 40 pounds, increased the pulse rate from 90 to 140. A total of 30 mg. (one-half grain), given in divided doses over a period of eighteen days to a woman weighing 112 pounds, increased the pulse rate from 75 to 130. Not only in rate but also in apparent vigor of the beat the cardiogram of a heart, after administration of the iodine com-

\* From the Mayo Clinic.

1. Kendall, E. C.: A Method for the Decomposition of the Proteins of the Thyroid, with a Description of Certain Constituents, *Jour. Biol. Chem.*, 1915, xx, 501.

2. Baumann, E.: Ueber das normale Vorkommen von Jod im Thierkörper, *Ztschr. f. physiol. Chem.*, 1895-1896, xxi, 319.

3. The physiologic activity referred to is the production of the so-called hyperthyroid symptoms, tachycardia, increase in metabolism with loss of weight and increase in nervous irritability. Some other constituents of the gland possess physiologic activity, but of minor importance.

pound, simulates a cardiogram of a patient with exophthalmic goiter.

What, then, is the relation of this iodine compound and the symptoms of exophthalmic goiter? Pathologic investigation has shown that the severity and duration of the symptoms are accompanied by definite histologic changes in the thyroid. It has been shown that in the severest forms of exophthalmic goiter the parenchyma is far more active than in the normal gland.

Analysis of 137 thyroids from exophthalmic goiter cases showed that, in those glands having a thin, watery secretion, the iodine content was very low, but as the secretion became thicker and less diffusible, the percentage of iodine increased.

These results point to two functions of the thyroid: One function is the manufacture of the iodine compound, and the other that of acting as a reservoir for this compound. We have no means at present of measuring the manufacturing capacity of the gland, but we do know that it is greatly increased in exophthalmic goiter. The reservoir capacity of the gland is obviously proportional to the iodine content. The total amount of iodine in the severest form of exophthalmic goiter averaged 7 mg., and the total iodine in glands in which the secretions had become thick and less diffusible was 35 mg. That is, the reservoir capacity had increased 500 per cent., and when it is known that 1 mg. a day of the pure crystalline iodine compound will produce marked toxic symptoms in a normal person, the important rôle played by the iodine compound in the production of symptoms of exophthalmic goiter is evident.

The separation in pure form of the iodine compound is the first necessary step in the further study, not only of pathologic conditions, but also of the normal physiology of the gland.

#### SUMMARY

1. By an alkaline alcoholic hydrolysis, the thyroid proteins are broken into many simpler constituents. These may be separated into two groups: the acid insoluble compounds are designated Group A; those acid soluble, Group B.

2. From Group A a pure crystalline compound, containing 60 per cent. of iodine, has been isolated. It appears to be di-iodo-di-hydroxy-indol.

3. Group B contains iodine in some unknown form of combination. It is a mixture containing amino-acid complexes and a low molecular weight.

4. Administration of A produces in the dog and in the human being a rapid increase in pulse rate and vigor, and increase in metabolism and nervous irritability. This physiologic activity is produced by the compound containing iodine in all stages of purity up to and including its crystalline form.

5. Given in excess, toxic symptoms are produced. The amount of the iodine compound required to produce toxic effects is exceedingly small.

6. In exophthalmic goiter two abnormal conditions exist. First, the secreting capacity of the gland is greatly increased and, second, the reservoir capacity of the gland is greatly decreased. The iodine compound plays an important rôle in the production of the symptoms of exophthalmic goiter.

7. The constituents of Group B produce no toxic symptoms, but in cases of cretinism, myxedema and certain skin conditions, they exert physiologic activity.

## THE AIMS OF THE ASSOCIATION OF AMERICAN PHYSICIANS\*

S. J. MELTZER, M.D., LL.D.

NEW YORK

It is not only customary, but it is by the order of the constitution, that the president opens the first session of the annual meeting by an address. I shall use the words of the first president of the association as a starting point for my remarks. President Delafield said:

We want an Association in which there will be no medical politics and no medical ethics; an association in which no one will care who are the officers.

I shall deal first with the last-mentioned remark. We still do not care who the officers are. It is the prerogative and the duty of the incumbent of the office of the presidency to express his views on subjects which concern the welfare of the association. Now I wish to say that in my opinion the members of the association shall care more than they do, who are their officers, and especially who shall be their president. In the course of our existence the constitution was so amended as to invest the president with autocratic powers, while his election gradually became, by mere custom, entirely undemocratic. I presume that not many of you know the exact procedure. The five councilors fill each year the coming vacancy in their ranks. The oldest councilor becomes vice-president and then president. While the recommendations of the council are formally submitted to your vote, I am not aware that they were ever voted down. In my opinion this oligarchic form of government harbors a danger. It may readily happen that the *progressive* majority of the members will be continually governed by entrenched *regressive* elements. I do not mean to imply that we are actually confronted with such a situation; I merely wish to call your attention to the possibilities which such an anomalous situation may have in store for you. I do not wish to offer any remedial suggestions; these must come from the members.

Having served as an officer of the association for the last seven years, I am in a position to make the agreeable statement that medical politics and medical ethics still play practically no rôle in the procedure of election to membership in the association. It holds true, in general, that each year of the numerous candidates the best men are elected to fill the vacancies. But I wish to state warningly that we are not entirely free from danger. I am not afraid that we shall ever elect to membership one who was convicted for a criminal act. But avoidance of coming in collision with the criminal code or even a strict compliance with the ethical code of the American Medical Association are not unrefutable evidences of highmindedness. Commercial success in practice of medicine, social standing and social relations, manipulated publicity, the familiar principle of "one hand washes the other" and evils of a similar character are the pernicious elements which may endanger the high standard of our association. I speak not merely from theory. As president, I am entitled to express the wish that the association should comprise not only the most gifted,

\* Remarks made at the opening of the thirtieth meeting of the Association of American Physicians by its president, May 11, 1915, Washington, D. C.