Special Article

THE BEST SOURCE OF IODINE (ORGANIC *VS.* INORGANIC) AS RELATED TO THYROID DISTURBANCES

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Historical study of iodine in relation to thyroid

HYPERTHYROIDISM, particularly endemic goitre, is prevalent throughout the world. It is more prevalent in some regions than in others. Since Baumann's(1) important discovery that iodine is a normal constituent of the thyroid gland, chemists have attempted to find its linkage with other molecules. Oswald(2), Hutchison(3, 4), von Cyon and Oswald(5), and many others have shown that iodine in the thyroid is bound with a protein molecule. Sufficient data are available to show that in a normal thyroid gland no inorganic iodine is present. The exact nature of the thyroid organic compounds containing iodine varies. Several workers, such as Romeis(6), Meyer(7), Kendall(8), Ingvaldsen and Cameron(9), Nürnberg(10), Weir(11), and Kendall and Simonsen(12), have shown experimentally that iodine does not occur in any one definite form. Some of them have indicated further that all of the iodine does not occur as thyroxin.

If the presence of iodine in the thyroid is a normal constituent, as has been shown by the above-mentioned workers, it may be reasonable to assume that the activity of the thyroid would depend on its relative quantity. Researches undertaken by Kendall *et al.*, as reviewed by him(13), tend to show that thyroid activity is proportional to its iodine content. Kimball *et al.* (14, 15) and Silberschmidt(16) produced some data which show the justification for the use of iodine in endemic goitre. For further details Kimball(17) may be referred to.

Iodine has not only been suggested to be beneficial in endemic goitre, but Plummer and Boothby(18), Loewy and Zondek(19), Neisser(20), Starr and Means(21), Cowell and Mellanby(22), Graham(23), Mason(24), Foster(25) and Breitner(26) have shown its value in exophthalmic goitre. Jackson(27), with reference to the primary treatment of exophthalmic goitre, writes thus: 'In my experience no single factor with the exception of iodine itself has proved of such valuable aid in the treatment of this condition'. The experience of Mosser(28) agrees with that of Jackson. It has been reported by Breitner(26) that iodine at once calms down the increased tonus of the sympathetic system, by which the hyper-sensitiveness is stopped. These claims may have been overdone somewhat, as is explained below.

All types of goitres cannot be treated successfully with iodine as shown by Kocher(29), Buford(30), Baker(31) and Evvard(32). All these authorities advocate the use of clinical methods. This they claim to be particularly true for exophthalmic goitre. There are some surgeons, however, who advocate the use of iodine along with, and without, clinical therapy, a subject outside the scope of the present thesis. It has been claimed by McCarrison*(33, 34, 35) that goitre may be produced because of some changes in the thyroid as a result of vitamine 'A' deficiency. It has been further found by Harris and Smith(36) that pathological conditions in the thyroid may be brought about as a consequence of vitamine 'C' deficiency. From the investigations of the above-mentioned authors, as well as from the contributions of Burget(37) and Bensley(38), it seems highly probable that there exists a relationship between diet (independent of the amount of iodine) and the thyroid activity. McCarrison, however, whose work is more fully supported by data, has recently clearly stated his view when he expressed the belief that goitre is due to the relative supply of iodine. Fraser and Cameron(41) and Rabinowitch(42) recognized both iodine and vitamine as essential factors in the prevention of goitre. From these investigations a question may be raised: Is there any relationship between the amount of iodine and the synthesis of vitamine 'A' in plants in Nature? As far as the writer is concerned, there are no data available at present to answer this question. The writer, however, has undertaken this study in co-operation with the Nutrition Department (School of Home Economics), Iowa State College. It has previously been shown by Malhotra(43) that there is a relationship between some inorganic fertilizer constituents other than iodine and the synthesis of vitamine 'A' in several plants.

From the chemical, physiological, clinical and pathological literature on endemic goitre, too extensive even to abstract here, it seems reasonably well established, at least at present, that iodine is indispensable for the prevention and probably cure of endemic goitre. Its beneficial influence in this connection may be manifold. This need not be discussed here, since it is proposed to submit a fuller report comprising the clinical, biochemical, physiological and nutritional data for publication elsewhere at an early date.

Iodine also affects the body in certain other direct and indirect ways. Plummer(44) stresses its influence on the appearance and on the nervous system. Hoskins(45), Cameron and Carmichael(46, 47, 48) and Simpson(49) think that iodine may stimulate growth and development, because lack or decrease of iodine brings about a loss of thyroid function, which in early life is followed by retardation of growth. Data have been obtained by Terry(50), Birchner(51), Hoskins(52), Lim *et al.*(53), Nakao(54) and Hammett(55, 56) that the growth of bones is directly stimulated by thyroxin. Thus according to all indications, the liberal use of iodine must be of considerable importance for more than one metabolic function of the body.

The status of various types of inorganic iodine

What form of iodine is most efficient and how can it be obtained? The best method of supplying iodine deficiency has undergone a series of changes. A suggestion has been made by Little(57), Quimby(58), Longfellow(59), Sherman(60), Ellms(61) and others that iodine may be directly added to water supplies. The writer(62) has pointed out, and was later supported by others, that this is not a satisfactory means of iodine supply. He raised three serious objections, namely:—(*a*) Only a very small portion of the city water supply is used for drinking purposes, perhaps about 10 per cent. Thus it is conceivable that an enormous waste of iodine would make this method rather an expensive one. (*b*) The taste of water treated with iodine as sodium iodide or potassium iodide is very disagreeable. (*c*) In most of the rural districts, particularly in India, the source of water supply is direct from the well. This makes it doubly hard adequately to control its iodine content. Experience with Indian conditions shows that the simplest, most readily accessible and cheapest method alone would be satisfactory. Oleson(63) and others conclude, from the vital statistics obtained, that goitre is frequently found in sparsely populated districts (such as rural areas). Administration of iodine in the form of tablets has been preferred by some, but this also has disadvantages.

Rick(64), von Fellenberg(65), Eggenberger(66) and several others have recommended the use of iodized salt. Since such a salt is commonly used at present in most civilized countries, and since several commercial

* The writer thanks Colonel McCarrison for some suggestions and communications.

processes of manufacturing it have been developed, some points which previously have been overlooked may be worth mentioning now. It has been estimated by Miss Lewis(67) that, on the whole, less than 5 per cent. of the total salt is actually taken into the body without boiling or cooking. It has also been shown by Malhotra(68) that iodine combines easily with inorganic compounds but splits off just as readily. Such a difference between the organic and inorganic iodine can be well appreciated, based on the ionic theory. The tendency of iodine in this respect is almost the same within or without the body. Its active nature is similar to the characteristic dynamics of the other members of the halogen series.

On the other hand, iodine combines but slowly with organic molecules, at least with carbohydrates, proteins and fats. However, after such a combination it is held more firmly, as was indicated by the quantitative analysis of several specially treated economic plants for higher iodine storage before and after boiling. The same was found to be true after it had been acted on by the metabolic activities of the body. For instance it was found in many cases that iodine (as a part of carrot protein) was eliminated in the urine and fæces 10 to 15 times slower than similar iodine in combination with sea salt. Thus the experimental evidence does not support the suggestion that a proper amount of iodine can be held in the body by means of salt (or any other form of inorganic iodine) for the normal physiological functions of the thyroid gland.

Now there are a number of workers who agree with the writer in the facts mentioned above, particularly McClendon (recent years) and his co-workers at the University of Minnesota, and Remington and his associates in North Carolina. At present there seems to be but little support for administering inorganic iodine for the satisfactory and effective prevention of endemic goitre. These facts do not underestimate the value of iodized salt in the prevention of goitre. They are simply meant to show that this form of iodine is not without several drawbacks and that there is plenty of room for improvement. For instance, stable colloidal inorganic iodine, if it could be prepared, may be promising.

The sources of organic iodine and their importance

Broadly speaking, there are two sources of organic iodine * known at the present time, namely, from animal products such as milk and sea foods of different kinds; and from plant products such as vegetables, fruit and cereals. The latter have been produced and advocated by the writer during the last four years. The iodine content of both can be increased materially by artificial means. McClendon(69) has increased the iodine content of milk. However, in this state it is more in skim milk than in the fat particles, a rather undesirable feature. All the iodine is not recovered from milk, because a part is utilized by the animal body for its own thyroid activities, and a still greater portion is eliminated with the urine as a waste product. Therefore, iodine obtained from milk by feeding dairy cattle with seaweeds, such as kelps (which is practicable only near the seashore) is rather an expensive and unsatisfactory source.

Animal sea food such as lobster contains a definite range of iodine content. Even if this source of supply contains a higher percentage it is not always available without some changes (slight decomposition or putrefication), especially in areas away from the sea coast. Assuming it could be shipped to localities away from the coast, it is very doubtful if it could be made available to the bulk of the population because of their food habits. At times financial conditions (particularly in India) would not permit its continuous use. At any rate it seems to the writer, based on his experience in the rural areas of India and the United States of America, that this method of organic supply is not a feasible one, at least to the public at large.

Thus it would seem that the last, and probably the best source of organic iodine, for the present at least, may be vegetables, particularly root crops. The writer(62) as well as Remington, Culp and von Kolnitz(70), have shown that vegetables grown under natural environmental conditions, even in the so-called non-goitrous regions, contain insignificant amounts of iodine. It is possible, however, that the iodine content of the crops can be increased artificially. The writer(62), as well as Pfeiffer and Courth(71) (from Germany), have been able to increase the iodine content of several crops. The German workers have accomplished this end by adding iodine to the fertilizers, while the writer obtained similar results by adding iodine directly to the soil and determining its concentration in the plant and the soil. In another series he(72) controlled the hydrogen-ion concentration of the medium for the maximum permeability and diffusion of iodine into the plant root membranes, which seem semi-permeable. Recently the writer(73) has developed another method by means of which seeds may be soaked. A plant grown from the treated seed may yield a higher iodine content. The former method may be exploited for growing vegetables rich in organic iodine, while the latter may be useful in obtaining cereals of high iodine content.

Methods used in obtaining higher yields of organic iodine from plants

Two distinct methods of growing plants for high iodine content have been developed by the writer during 1926—31. The first one is applicable for vegetables and truck crops, and the second for grains. It will later be shown why it was necessary to make such a distinction between these two procedures.

Almost all truck crops can be increased with reference to their iodine content. However, it has been found experimentally that root crops, such as carrot, sugar beet, sweet potato, Irish potato, radish and so forth, can absorb and retain more iodine than vegetables other than the root crop type. This peculiar behaviour of root crops is not fully understood at present. However, microscopic studies have suggested that iodine is stored in the active parenchyma cells.

Vegetable seeds may be so sown in the soil with the addition of potassium iodide as 5,000—8,000 parts per billion. Later it was found that seeds should be sown in an ordinary soil. From the appearance of the seedlings until maturity of the plants, iodine solution (such as potassium iodide) may be added once every week. The total iodine content added each time should not exceed 300 parts per billion. This method is more satisfactory. The hydrogen-ion concentration of the soil may be adjusted so that the pH remains at a range somewhat between 5.5—6.5. Many simple methods of determining the hydrogen-ion concentration have been developed within recent years. Thus it is unnecessary to describe them here. The writer(72), Powers(74) and others have shown that this pH range is favourable for the maximum growth of most plants. The data obtained by the writer also indicate that the maximum iodine intake also takes place within the same pH range.

The results (without adjusting the hydrogen-ion concentration of the soil) are shown in Table I. A comparison of the iodine content of plants grown with and without the addition of iodine in the soil shows a higher iodine content in favour of the soil with the additional iodine. The accumulation of iodine in all kinds of crops used by the writer are illustrated in Fig. 1, which is self-explanatory. These investigations(75) show that, in the main, most of the iodine is accumulated in the parenchyma and the sclerenchyma cells. Fig. 2 shows the photomicrograph of a tomato

* The term organic iodine as used in this article refers to the atomic iodine combined with an organic molecule.

stem. The black spots in the central cells (parenchyma) and near the vascular bundles present the distribution of iodine as determined by the well known starch test. No depressing effect of iodine on the plants up to 16,000 parts per billion, with the exception of tomato, could be noted by the writer. Even the latter plant did not show any iodine injury between 5,000—8,000 parts per billion of iodine in the soil.

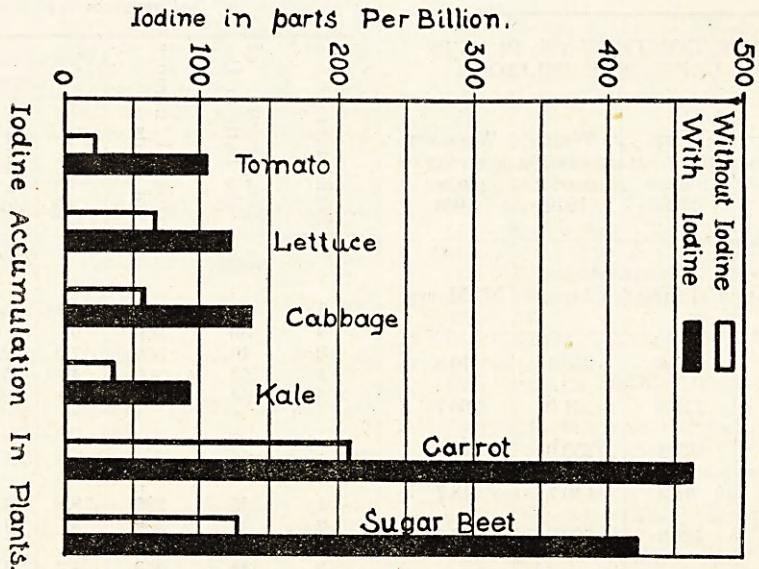

Fig. 1.—Chart showing the iodine content of different plants grown in soil with and without additional iodine. The data for 1926 only have been plotted.

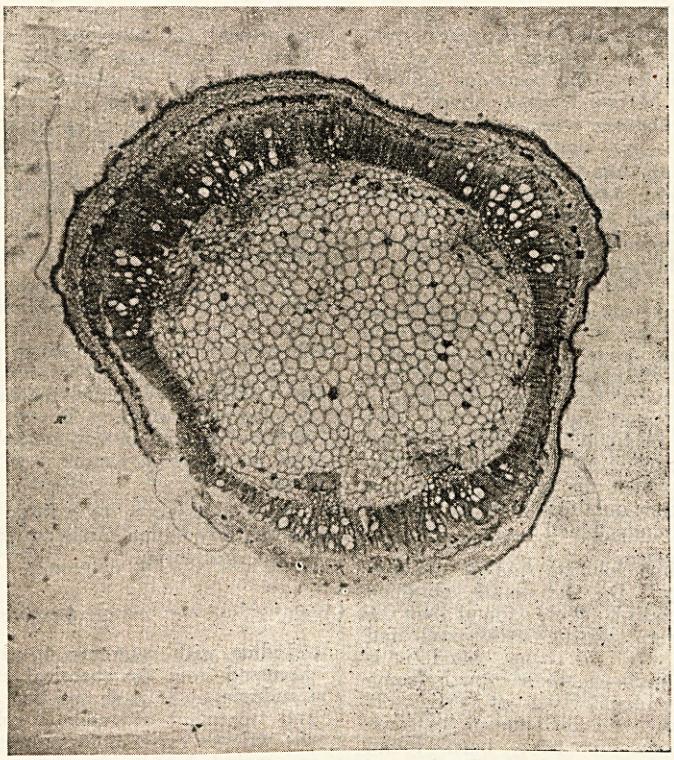

Fig. 2.—Photomicrograph of a cross section of tomato stem. Note the distribution of iodine. For details refer to the text.

TABLE I

Iodine content of plants grown in soil with and without the addition of iodine

Kind of plants	IODINE CONTENT OF PLANTS IN PARTS PER BILLION			
	WITHOUT ADDITIONAL IODINE 1926	WITH ADDITIONAL IODINE 1926	WITH ADDITIONAL IODINE 1929	WITHOUT ADDITIONAL IODINE 1930
	Grown at: Rio Vista	California	Chicago	St. Marys
Tomato ..	23.3	105.8	253.1	16.8
Lettuce ..	65.3	121.8	241.0	60.7
Cabbage ..	59.0	137.4	259.0	20.5
Kale ..	37.9	94.8	140.7	18.7
Carrot ..	209.3	463.3	668.8	132.6
Sugar beet	128.0	..	..	..

Note.—(1) The results recorded here are based on an average of duplicate samples of 4 plants of each kind.

(2) The soil in California was 18 miles from the Pacific Coast. Perhaps this is why it had more iodine (850 parts per billion) than at St. Marys, Kansas, about 1,000 miles from the sea coast.

(3) In the soil to which iodine was added, the reading for the total amount was always approximately 5,000 parts per billion unless otherwise stated.

(4) The 1926 experiments were conducted in soil with pH between 5.5—6.5.

The iodine content of cereals and other farm crops may be increased by soaking the respective seeds in a dilute solution of potassium iodide (0.03—0.05 per cent.) for 20—30 hours at room temperature, about 20°F. The seeds obtained at maturity of the crop may have a higher iodine content. It may be pointed out that in this case iodine most probably combines with the proteins and carbohydrates of the grains. The mechanism by means of which the growing plant can allow the entrance and accumulation of extra iodine ions from the soil is still unexplained.

Do seeds soaked in iodine solution lose or decrease their germinating capacity? Do the plants obtained from such seeds grow normally? It was found that the germinating capacity of corn, wheat, oats, peas and beans did not decrease. On the other hand, it is probable that iodine may influence their growth (some more than others) by its disinfecting properties. If this is true it may increase seed germination to some extent. In fact this seems to have been found experimentally. Table II shows the germination of corn after soaking the grains in 0.05 per cent. iodine solution and distilled water (as control) for 60 hours at different temperatures. It would seem from the data that iodine is not injurious to seeds at the lower ranges of temperature (field conditions) used in this experiment. Neither the seedlings nor the mature plants showed any signs of iodine injury or retardation, at least not apparent enough to be detected by observation.

TABLE II

Germination of the Zea Mays (corn) seeds after soaking in 0.05 per cent. of iodine solution and distilled water at various temperatures

Serial number	Temperature of the bath in C.	Original number of seeds	PERCENTAGE OF SEEDS		Characteristics of the seedling
			Germination	Non-germination.	
	Iodine				
1	25	260	99	1	Best growth
2	30	260	91	9	Healthy growth
3	40	300	78	22	Ordinary growth
4	50	300	49	51	Adverse growth
5	60	280	3	97	Mould
	Water				
1	25	280	89	11	Seedlings
2	30	300	89	11	Healthiest and alike.
3	40	250	87	13	Normal growth
4	50	260	53	47	Poor growth
5	60	260	8	92	Mouldy growth

The need for further co-operative research

From what has been said above, it would seem that at present the best source of iodine is from plants. Methods have been developed by means of which the iodine content of plants can be increased materially. It must be granted, however, that the best methods have not yet been attained and that there is room for further improvement. One thing is certain, however, that these or similar methods will be used more and more because they are simple, cheap, practicable in both rural and urban areas, and at the same time they are more effective than the methods now used or advocated.

What influence these findings may have on the co-operation of Botany and Medicine, only the future can tell. It seems, however, that vegetables grown for the prevention of endemic goitre will require iodine mixed in fertilizers, or in such form as may be found best in the future. We have reached a stage in scientific development where a hearty co-operation among the workers engaged in various fields must be desired more and more, which means a great deal to humanity at large.

It is a pleasure to acknowledge the help rendered by Mr. Ray Glynn, Assistant in the Biology Department of this institution.

Summary

Iodine with reference to thyroid gland function is discussed from the chemical, physical and physiological standpoints. It is shown that its use in the prevention and treatment of endemic goitre is inevitable. From the writer's experiments as well as from other data, it is concluded that inorganic iodine or iodine in combination with inorganic compounds has certain serious disadvantages. In this respect, addition of iodine to water, iodized salt and iodine tablets have been considered from various standpoints.

It has been pointed out by recent researches that atomic iodine in combination with organic molecules is more satisfactory, permanent, and hence more effective in the prevention of endemic goitre. Two sources of

iodine, namely: from animal products, such as milk and sea food, and from plant products, are discussed. The merits and limitations of each are explained. It seems that iodine from plants may be the better source because it is comparatively cheaper, is easily accessible in any locality, and is more satisfactory in its more permanent effects. Two distinct methods of increasing iodine content of (*a*) vegetables and root crops, (*b*) cereals and other farm crops are described. Some additional data to that effect are also presented. The need for further co-operative research is also pointed out.

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