Editorial.

IODINE IN NUTRITION.

RECENT research has clearly demonstrated the importance of the mineral constituents in a diet. A proper balance, both qualitative and quantitative, of these substances is just as necessary from a physiological point of view as a due supply of proteins, fats, carbohydrates and vitamins. Mineral constituents are present in practically every food taken in an ordinary diet, and it has usually been taken for granted that they are normally supplied in due amount and variety, and disturbances in animal life have not been attributed until comparatively recent years to a shortage of mineral matter.

Iodine has been shown to be absolutely essential for the maintenance of the physiological balance of the animal organism. The most marked disturbance in men and warm-blooded organisms is associated with the thyroid gland, which seems to control the iodine exchanges of the body.

Dr. Orr and Dr. Leitch have compiled a report on Iodine in Nutrition for the Rowett Research Institute, Aberdeen, which has been published by the Medical Research Council. In the historical survey they point out that iodine was discovered in marine products by Davy in 1815, and by Staub and Fyfe in 1819. In 1820 Coindet, a physician in Geneva, suggested that the beneficial effect of marine products in goitre might be due to the iodine they contain. He found that the administration of iodine to patients with goitre led to the disappearance of the goitre, but in some cases toxic symptoms followed the treatment. Numerous physicians confirmed Coindet's results and d'Espine estimated the minimum curative dose at 0·5 milligramme a day.

In 1849 Prévost, who was already familiar with the therapeutic use of iodine, put forward the suggestion that goitre was due to deficiency of iodine and bromine in drinking water. In 1850 Chatin, a Professor of Pharmacy in Paris, found that iodine is universally present in nature, but the amounts in different soils, water, and plants vary. In goitre districts the iodine content of water and food was low, and he advanced, probably without knowledge of Prévost's suggestion, the hypothesis that goitre is due to deficiency of iodine.

The French Academy of Science appointed a commission which confirmed the universal presence of iodine in nature, but could not accept the idea that such small amounts of iodine would have any effect on the human body. As a result of the commission's findings Chatin's theory fell into discredit in scientific circles.

In 1855 Koestl proposed the use of iodized salt in Austria; and Lambroso, in 1859, recommended that as a means of preventing cretinism, goitrous individuals of marriageable age should be treated with iodine. In 1860 an experiment with iodized salt was carried out in three French Departments: school children, in addition to the salt, were given one centigramme of potassium iodide per day in tablets. These doses caused toxic symptoms and the experiment was abandoned.

In 1895 Baumann discovered iodine in the thyroid gland. He then set out to determine whether goitrous glands contained as much iodine as normal glands, and found that the percentage of iodine in goitrous glands was much reduced. This discovery was followed by a revival of the prophylaxis of goitre by iodine, and in the new experiments over-dosage was avoided. Galli-Valerio and Grassi recommended that school children should receive one drop of tincture of iodine per day, and in the district of Valtellina excellent results were obtained. In the Canton Appenzell iodized salt became general in 1922, and by 1925 it was reported that no more cretins were born and congenital goitre had practically disappeared.

In America, Marine determined the iodine content of thyroid glands in domestic animals and confirmed Baumann's discovery that goitrous glands contain less than the normal. In 1918 he published the results of his experiments on school children in Akron, Ohio, showing a reduction in the size of goitres following the administration of potassium iodide.

One of the chief difficulties in iodine investigations has been the lack of an exact method of determining the small quantities of iodine in plants and animal tissues, and it is only within the last two or three years that sufficiently accurate methods have been devised. Probably the best of these are modifications of v. Fellenberg's. By his method v. Fellenberg was able to show that the excretion of iodine in urine was less in the inhabitants of goitrous areas than in those of goitre-free areas.

In Part II of their paper Drs. Orr and Leitch give a detailed account of the distribution of iodine in nature. Though very widely distributed it is present both in plant and animal tissues in very small quantities, and the common method of reckoning is in millionths of a gramme, and for this unit the symbol γ is used. It is only in a few substances, such as the saltpetre deposits of Chile and Bolivia and in some sponges, that concentrations up to 0·1 or 0·2 per cent occur.

The amount of iodine found in soils varies from 600 γ to about 6,000 γ per kilogramme and the contents appear to be greater than that of the rocks from which they are derived. Plants have a great power of concentrating iodine, and the retention of iodine in the resulting humus of soil, while the other constituents of the weathered rock are carried off in drainage water, is one of the main factors in increasing the percentage of iodine in soils.

As regards fresh-water supplies, Chatin found that water from formations rich in lime and magnesium contained very little iodine. Von Fellenberg found 0·38 γ per litre in water from the Emme. The Arno above Florence contained 0·75 γ per litre. Orr, Godden and Dundas found in the River Dee (Aberdeen) from 0·5 to 0·71 γ per litre.

Sea water contains from 17 to 18 γ per litre. Seaweed contains amounts up to 2,640,000 γ per kilogramme dry substance.

In water supplies in America amounts of iodine varying from 0·01 to 9·5 γ per litre have been found. In twenty water supplies in England and Scotland, analysed at the Rowett Institute, the amount varied from 0·05 γ to 4·2 γ per litre.

Sea plants are much richer in iodine than fresh-water plants, and the latter are in turn richer than land plants.

Fyfe, of Edinburgh, was the first to demonstrate the presence of iodine in animal tissues and, as we have already mentioned, Baumann, in 1895, found iodine in the thyroid gland.

The iodine intake is the most important factor affecting the percentage of iodine in the thyroid. There is a seasonal variation in the iodine content of the thyroids in ruminants, a maximum in the autumn and a minimum in spring. This is probably correlated with the amount of iodine in the pastures. Baumann noticed that in sheep and humans there was an inverse relationship between the size of the thyroid and the percentage of iodine. This was confirmed by Marine, Lenhart, Aldrich and Martin. Glands above a certain weight are usually eliminated in selecting thyroids for the preparation of a standard Thyroideum siccum.

According to Orr the average figure for human thyroid iodine is 7·8 milligramme, which would be about 60 per cent of the total body iodine.

Iodine is an unfailing constituent of milk, and the content depends to a great extent on the intake of iodine and may be raised to a very high level.

The effect of iodine in plant metabolism is to stimulate growth. The activity of nitrifying bacteria is increased, and the assimilation of nitrogen promoted.

In studying the influence of iodine on animal metabolism it is difficult, and in many cases impossible, to distinguish between the direct action of iodine ions *per se* and their indirect action through their influence on the thyroid secretion. The administration of potassium iodide to animals appears to stimulate growth. In the case of calves iodine up to 0·05 milligramme per day has a beneficial effect, but beyond this amount toxic effects are produced. In pigs, however, no toxic effects were noticed with much larger doses.

There is little information of the effect of iodine on the growth of children, and what we have comes from goitre areas. In Cumberland Fraser found that after iodine treatment there was "in practically every case a marked improvement in health and physique, a gain in weight, in energy and in working capacity."

A comparison of the effects of iodine and thyroid secretion on growth shows that the lack of either will result in subnormal growth. In animals excess of thyroid both limits growth and causes abnormal development. This, however, is not due to the iodine contained in the thyroid secretion. The effects of the thyroid secretion are more complex than those which result from the presence of iodine ions.

It appears that iodine *per se* is not the active agent in inducing metamorphosis, but is merely an essential constituent of a compound which under normal circumstances is elaborated by the thyroid and which in the absence of the thyroid can be elaborated by the pituitary.

Experiments have shown that regulation of the basal metabolic rate is one of the main functions of the thyroid. In the absence of thyroid secretion either in thyroidectomized animals or in myxœdema, the rate is subnormal, and the administration of the secretion raises the rate both in normal subjects and in cases where there is lack of thyroid secretion. The rise in the rate is due to increased carbohydrate metabolism. There is experimental evidence that iodine tends to lower the basal metabolic rate and so causes increased sugar tolerance in diabetes complicated by exophthalmic goitre. Whether the same is true in diabetes uncomplicated by hyperthyroidism is unknown.

Drs. Orr and Leitch then give detailed information on the effect of iodine on various organs and tissues other than the thyroid. They say that the available information suggests that iodine stimulates intestinal movements and excessive doses cause diarrhœa. Thyroid appears to have a somewhat similar effect. Most of the observations with thyroid have, however, been made on subjects with abnormal glands.

Veil and Sturm, in 1925, found that in normal blood sixty-five per cent of the iodine is in organic combination. They found that 0·5 gramme of potassium iodide raised the blood-iodine from 15 γ to 1308 γ per 100 cubic centimetres, but the normal level was reached again at the end of forty-eight hours. In one case the organic iodine in the blood was found to decrease with the rise of the total iodine, and remained at the lower level for twenty-four hours. This finding may offer an explanation of the beneficial effects of inorganic iodine in exophthalmic goitre.

At the Rowett Institute, Orr and Leitch found the blood-iodine falls after thyroidectomy. Thyroid administration increases the red blood-count, but an overdose may produce symptoms of thyroidism.

Orr found in rabbits receiving a small daily dose of iodine a marked increase in the coagulability of the blood as compared with the controls.

It is a well-established fact that thyroid administration increases the pulse-rate both in normal and hypothyroid cases. Blalock and Harrison, in 1927, found that thyroid feeding in daily doses of 0·7 gramme for four to six weeks caused an increase of the cardiac output of 80 to 120 per cent. The oxygen consumption was increased sixty to eighty per cent. After omission of thyroid the rate of oxygen consumption returned to normal more rapidly than the cardiac output. These results seem to indicate that the thyroid may have a specific effect on the myocardium. Thyroidectomy caused a diminution of cardiac output greater than the decrease in oxygen consumption.

As regards the sex organs, experiments on animals appear to show that the thyroid is necessary for their normal growth and function, but excess of thyroid interferes with sexual development and activity. The effect of iodine is similar. As regards the mammary glands, Drs. Orr and Leitch found at the Rowett Institute no harmful effect on milk secretion of moderate doses of iodine. Any well-balanced ration will probably contain sufficient iodine, and it is unlikely that further addition will stimulate the secretion of milk.

In the last sections of their paper Drs. Orr and Leitch give a summary of the changes in metabolism and structure of the thyroid in goitre, the use of iodine in the treatment and prevention of goitre, and the iodine requirements in animals and in man.

They describe briefly the changes which take place in the normal thyroid from infancy to adolescence. The increase in size in the thyroid at puberty is due both to accumulation of colloid material and proliferation of epithelium.

In 1896 Baumann isolated from the thyroid an organic iodine-containing compound (thyroidin) which he showed had the physiological properties of the whole gland. In 1919 Kendall isolated in a crystalline form a substance which he called thyroxin. Boothby and Sandiford, in 1924, showed this substance had the main physiological properties of the thyroid.

Harington improved the method of isolating thyroxin and gave it the formula $C_{15}H_{11}O_4NI_4$; he was also successful in synthetizing the substance. It was thought at one time that the physiological effects of thyroxin (hormone) were due to the organic portion of the molecule, but the work of Abelin has shown that the presence of iodine in the thyroxin molecule is necessary for its full physiological activity.

Tatum and van Dyke found that in the thyroid of animals the colloid contained more iodine than the cells, and van Dyke found this to be true for human thyroids. The colloid was thought to be absorbed by the lymph, but according to Carlson and Woelfel and Hicks, it is probably by the blood-stream. The transition from the colloid-rich to the colloid-free condition may be extremely rapid. There is a relationship between the thyroid and ovarian function which requires a periodic mobilization of iodine and a depletion of the iodine store. Farrant has shown that there is a rapid mobilization of thyroid colloid in response to certain acute infections, notably diphtheria and measles, with a consequent drain on the iodine store of the body.

In simple goitre the structure and mode of development of the thyroid are normal, but the entire process of growth and colloid accumulation is exaggerated. Adenomata occur equally in the normal and goitrous gland; the only essential difference is the rate of growth. According to Aschoff and Holst, they approximate in nature to new growths and form the basis of most malignant tumours of the thyroid. Attempts have been made to ascertain whether the secretion of goitrous glands is normal in quality and amount. In thirteen cases of adenomatous goitre Weir found the amount of iodine present as thyroxin was reduced in proportion to the total iodine content.

The districts in which goitre occurs are usually mountainous, but not all such districts are affected. In New Zealand goitre is most frequently associated with river beds, and the same association is seen in America in the region of the St. Lawrence and the Great Lakes.

Goitre in domestic animals appears to occur in the same districts as goitre in human beings.

The low percentage of iodine content in goitrous glands suggests that the iodine intake in goitrous areas may be low. A comparative study of the iodine contents of human foodstuffs from goitre areas and non-goitre areas supports this view. The difference in the daily intake has been found to be about 18 γ in Switzerland and about 15 γ in New Zealand.

The rôle of iodine in the treatment and prevention of simple goitre also affords evidence that deficiency of iodine may have a causal relationship to overgrowth of the thyroid.

Excess of calcium in drinking water and food and the contamination of water supplies with micro-organisms have been supposed to have an effect in the production of goitre. But there is no real evidence to show that calcium has any influence on the growth of the thyroid, and the experiments of the Swiss Goitre Commission gave no support to the theory that goitre is due to the ingestion of contaminated water or food. Such a theory is also inadequate to explain the age and sex distribution of the disease. Such infections and toxæmias, by depleting the thyroid of iodine, might contribute an iodine deficiency.

We have already referred to Marine's work on the treatment of goitrous animals and the success which attended the treatment of children in Ohio; and to the use of iodine for goitrous children in Switzerland, New Zealand and parts of England. The most recent results in Swiss schools and in Austria showed similar beneficial effects following the administration of iodine. Summarizing the results, Drs. Orr and Leitch say that in the vast majority of cases administration of iodine arrests the growth and reduces the size of goitrous glands. The effect is greater the earlier the treatment is applied. After puberty the efficacy of the treatment is reduced, and after twenty is practically confined to soft parenchymatous glands, hard and nodular goitres giving little or no response. The use of iodized salt by pregnant women prevents the birth of goitrous children.

Toxic symptoms described as hyperthyroidism have been stated to follow the administration of iodine in adults. A critical examination of the cases has shown that the symptoms were mainly caused by excessive doses of iodine and reliable observers have never seen toxic symptoms following the use of iodized salt.

From experiments that have been made by v. Fellenberg and others, it may be deduced that the minimum amount of iodine required for equilibrium in the adult male is about 15 γ per day, and in a child about 50 γ.

Since exercise and excitement increase the requirements a liberal margin of safety is necessary, and on analogy with the requirements of other mineral substances, the minimum daily requirements may therefore be about 45 γ for an adult and 150 γ for a child.

The doses of iodine which were given to prevent goitre by Kimball and and Marine at Akron, eleven milligrammes a day, and by Hercus, Benson and Carter in New Zealand, seven to twenty-one milligrammes a day, are far outside the limits of physiological intake. Marine now considers five to ten milligrammes a week is sufficient for preventive purposes, and a somewhat higher dose for curative measures. In 1921 Klinger, in Zurich, gave fifteen milligrammes a week for eighteen months and in subsequent work the dosage has been lower.

Hunziker and Eggenberger, in their Appenzell experiments, used a salt containing one gramme of potassium iodide to 100 kilogrammes salt. This gives a daily dose of 0·1 milligramme if the salt is used at table only. The salt (1-100,000) was found to be eminently successful in the treatment of goitre in school children, and in the prevention of congenital goitre. Since 1922 no children with congenital goitre have been born from women using iodized salt for at least five months of the pregnancy. If it is used for cooking, baking and all purposes, then a salt of half this strength, 1-200,000, would be sufficient to give the same daily dose. This is the dosage adopted by the Swiss Goitre Commission.