ENDOCRINES IN THEORY AND PRACTICE

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THE PROBLEM OF ENDEMIC GOITRE

BY

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There are two types of endemic goitre, with many transitional forms between them, differing in their histological features, in their distribution, and in the constitutional states produced by or associated with them. It can hardly be doubted, so marked are these differences, that the two types differ also in their aetiology.

Two Types of Endemic Goitre

The first is the classical type prevalent in mountainous regions, such as the Alps and Himalayas, occurring as a colloid-poor diffuse *parenchymatous goitre* in childhood, and as an *adeno-parenchymatous*, nodular goitre, with its degenerative forms in adults. The second is the *diffuse colloid goitre* prevalent in lowland regions, such as the plains of Central Europe, and in England. The geographical limits of these two types are not clearly defined. Both may occur together in the same locality, but in general the former predominates in mountainous and the latter in lowland regions. The former is rarely associated with hyperthyroidism or Graves's disease; the latter is commonly associated with both. The former is usually associated with congenital goitre, cretinism, deaf-mutism, and various grades of physical and mental deterioration; the latter is rarely associated with these congenital manifestations of the disease. The former, in its adeno-parenchymatous form, increases in incidence as age advances, attaining to its acme between the ages of 50 and 60 years; the latter is more prevalent about the age of puberty, lessening rapidly or gradually disappearing after the age of 25 to 30 years. Both vary greatly in incidence in different localities. In regions of high endemicity the two sexes are affected in approximately equal proportions. In regions of low endemicity the incidence is higher in females.

The Parenchymatous Type

The parenchymatous type is a true hypertrophy of the gland; hence the name, *chronic hypertrophic goitre*, by which it is sometimes known. In this state of sustained hypertrophy the excretion of the gland's hormone tends to predominate over the secretion and storage of colloid, hyperplasia is pronounced, and many new vesicles are formed. Overstrain, or it may be toxic action on the gland itself, ultimately leads to fibrosis, with the appearance in the organ of circumscribed areas of more or less solid glandular tissue (adenomata), or of colloid-containing follicles (colloid adenomata), or of both. The gland is constantly straining to satisfy the needs of the tissues for its hormone, but just falling short of doing so; consequently evidence of hypothyroidism is often to be seen in sufferers from this type of goitre, hyperthyroidism rarely or never. In the pregnant female this sequence of events may result in failure of the maternal thyroid adequately to satisfy the needs of her own tissues and those of the developing foetus for the gland's products,

especially when some additional burden (fright, worry, acute infections, or intestinal toxæmia) is placed on its resources. As a result the foetal thyroid is unduly stimulated and congenital goitre may arise in the offspring. Or the developing gland may be destroyed by overstrain and/or toxic action, with the production of cretinism. Such toxic action may be due to some unknown noxa or to poisons absorbed from the maternal intestine, as in the experimental production of cretinism (*vide infra*) by the oral administration throughout pregnancy of a watery extract of faecal material. The congenital manifestations of adeno-parenchymatous goitre are as much a feature of the endemic as the goitre itself.

Diffuse Colloid Type

The diffuse colloid type is one in which the whole gland is made up of follicles of diverse shapes and sizes, distended with, and distorted by, the accumulation of colloid within them. These follicles are lined with flattened epithelium, and evidence of antecedent epithelial hypertrophy and hyperplasia may or may not be present; usually it is. In normal circumstances the secretion of colloid with its storage in the follicles and the excretion of the gland's hormone—elaborated by special cells from the stored colloid—proceed in balanced adjustment one with the other. In diffuse colloid goitre some influence is at work which causes the former process to predominate over, or to outstrip, the latter. Following a period of hyperplasia and its cessation colloid may accumulate in the gland in large amount. This is the usual explanation of the diffuse colloid goitre; but it is not wholly satisfying. It presupposes alternating periods of iodine-want and iodine-supply—iodine being the outstanding substance which increases colloid storage. It appears probable that other factors may be concerned in causing the undue accumulation of colloid. One of these seems to be the excessive ingestion of calcium relative to iodine and/or phosphates, which has been shown to cause such accumulation in animals. The recent investigations of Stott (1933, 1934) and his collaborators in the United Provinces of India, where diffuse colloid goitre prevails, have again brought into prominence the importance of lime as a goitrogenic factor in that locality if not in others.

Colloid tends to accumulate in the gland when there is a deficiency of vitamin C in the diet, and this accumulation may result in the production of small goitres. In this condition the gland exhibits a tendency to diminution in alkalinity, suggesting that the accumulation of colloid may be related to concentration of H-ions within the organ. Finally, certain infections, as by organisms of the type of the bacillus of Koch, may cause colloid to accumulate in the gland (Thomas, 1935). These, then, are factors whose possible influence in determining the histological characters of goitre cannot be ignored, particularly as they may vary with locality and as variation in histological structure with locality is an outstanding characteristic of endemic goitre.

A Cause of Confusion

It would seem that some of the confusion in regard to the causation of endemic goitre may be due to the

failure to distinguish between these two types of the disease. A further source of confusion is the common practice of estimating the prevalence of goitre by surveys confined to school children. These surveys, conducted, as a rule, by visual methods of examination, clearly admit of many sources of error. It cannot be too insistently stated that unless some reliable index of the normal size of the thyroid gland is employed in making such surveys the incidence of goitre in school children may be greatly exaggerated, erroneous inferences may be drawn as to its cause, or its prevalence be proclaimed in localities where, in truth, it may be practically non-existent. Further, it is not generally recognized that during early life the thyroid gland normally grows more rapidly than the body as a whole and may exhibit this phenomenon as a visible swelling. Without a knowledge of this fact, and without some reliable means of measurement of the size of the gland (McCarrison and Madhava, 1932), physiological swellings may be mistaken for pathological enlargements. "If you can measure that of which you speak, you know something of your subject; but if you cannot measure it, your knowledge is meagre and unsatisfactory" (Kelvin).

Endemicity of Goitre

What determines the endemicity of goitre? In attempting to answer this question a distinction may be drawn between the cause or causes of the endemicity of goitre and the cause or causes of the incidence of goitre. Clearly the endemicity is determined by something that is definitely localized in the localities where goitre prevails. Up to the present time research has failed to reveal any *positive* agency to which the endemicity of the disease can be attributed. Of *negative* agencies the only one known to us, and likely to be so concerned, is deficiency of iodine in the soils, and in the foodstuffs produced upon them, of localities in which goitre prevails. McCarrison and Madhava (1932), as a result of their statistical study of all available data dealing with this question, came to the conclusion that "a low intake of iodine may, in certain circumstances of diet and hygiene, be a potent factor in predisposing to the occurrence of goitre, and may even be a determining cause of its endemicity." A low iodine-intake makes the operation of positive goitrogenic agents potentially possible; the first may determine its endemicity, the second its incidence.

It seems probable that in the attempt to establish an inverse relation between the iodine-content of soil, food, and water, and the incidence of goitre, we are again being led astray. There is no reason why such an inverse relation, though possible, should be invariable. For given a low-iodine intake the incidence of goitre will depend on the potency of the goitrogenic agents, or summation of agents, exercising their unhampered action in the absence of a sufficient intake of iodine to prevent it. There is nothing more certain in regard to goitre than that a sufficient intake of iodine, or more properly a sufficient absorption and utilization of iodine, does counteract the action of all goitrogenic agents at present known to us, with the exception of vitamin deficiency. In the absence of such agents a low intake of iodine may not, by itself, cause goitre, while their presence will result in its occurrence; and if they be present in exaggerated degree they may even overcome the anti-goitrogenic action of a relatively high intake of iodine. It becomes important, therefore, to know what these goitrogenic agents are and to continue the search for others. Even though future research may reveal the existence of a "goitre-noxa" to which both endemicity and incidence of the disease can be

related, this noxa, too, is amenable to a high degree of control by the prophylactic use of iodine. In answer to the question above propounded it may therefore be said that, while there is much evidence connecting the *endemicity* of goitre with a low iodine-intake relative to goitrogenic agents, there is no sufficient evidence to justify the supposition that an inverse relation exists between the *incidence* of goitre and the amount of iodine available in a district.

Goitrogenic Agents

These are: (1) faulty diet; (2) chemical substances; (3) insanitary conditions; and (4) infections.

DIET

The more perfect the constitution of the diet the more normal the frequency distribution diagram of thyroid weights and sizes, the more stable the thyroid gland in point of size, and the less likely is goitre to arise. The faults in diet that may give rise to goitre in animals under experimental conditions, and presumably therefore in man, are: (A) Excesses of certain substances—fats, fatty acids, and lime. (B) Deficiency of certain substances—iodine, vitamin A, vitamin C, protein (in association with vitamin A deficiency), and phosphates (relative to an excess of lime). (C) Goitre-producing substances—cyanogen compounds—in certain foodstuffs such as cabbage. (D) Insufficiency of certain anti-goitrogenic substances, of unknown nature but other than iodine, present in certain fresh plants such as green grass, alfalfa, the expressed juice of steamed cabbage, and in sprouted legumes and carrots. All these faults can be remedied and their goitrogenic action counteracted by the use of a properly constituted diet containing adequate supplies of iodine.

Among foods rich, or comparatively rich, in iodine are those derived from the sea, eggs, goat's milk, lettuce, the outer leaves of cabbage, carrots; and, among condiments, ginger, black pepper, cumin, coriander, and cloves. Sophisticated cereal foods, pulses, tubers, root vegetables, meat, sugar, jam, etc., are, in general, relatively poor in iodine. The iodine-content of foodstuffs varies within wide limits in different localities. Thus that of green vegetables of different kinds may vary between 4γ and 77γ per kilo, that of cereals between 18γ and 65γ, that of pulses between 22γ and 33γ. The minimum requirement of iodine is said to be 45γ daily for adults and 150γ for children of school age; yet in the goitre-free locality of Coonoor, S. India, the average daily consumption of iodine by vegetarian schoolboys was found to be only 31γ, or 11.3 milligrammes per annum, illustrating the fact that in the absence of positive goitrogenic agents a relatively low iodine consumption may not be associated with the occurrence of goitre.

CHEMICAL SUBSTANCES

Among those capable of causing goitre in animals under experimental conditions are calcium, boron, silica, tellurium, organic acids, amines (Pighini, 1933), and cyanides (Webster, 1933). The goitrogenic action of all these substances is annulled by the administration of iodine. The continued application of carcinogenic petroleum and shale oils or tars to the skin of mice causes thyroid enlargement in a proportion of them (Twort and Twort); it is preventable by the enrichment of the diet. Anterior pituitary gland extract causes marked thyroid hyperplasia when injected for a few days into healthy animals, thus indicating the close interrelation between the thyroid and pituitary glands. Cyanide appears to act in the production of goitre by depressing tissue oxidation, with con-

sequent demand for an increased production of thyroxine and for an increased supply of iodine to meet this increased production. How far these observations in animals have a bearing on the problem of endemic goitre in man is still unknown.

The view, expressed by Repin in 1908, that radio-activity in soils and waters of regions where endemic goitre prevails is a goitrogenic factor has lately been revived, though goitre is said to prevail in certain localities where no such radio-activity exists. But that is no reason why it should not exert a goitrogenic action in regions where it does exist. A re-examination of the question appears to be called for.

INSANITARY CONDITIONS

Insanitary conditions involving the contamination of the food and drinking-water by human and animal excreta is a potent goitrogenic agent in localities where the iodine content of the soil is low (McCarrison, 1917). In regions (Himalayas) where these conditions prevail endemic goitre and its congenital manifestations are rife. The incidence of the malady in its adeno-parenchymatous form has been found to increase in such localities with increasing impurity of the surface waters used for drinking purposes. Goitre has been produced, under experimental conditions, in man by the administration for some weeks of the residue left in the candle of a Berkefeld filter after filtration of this water. The substitution of a bacteriologically pure for an impure water supply has caused the disappearance of the disease. Animals confined in insanitary cages and fish confined in filthy tanks or ponds tend to develop goitre, which can be prevented by the additional provision of iodine. The scrapings from the interior of such tanks has been shown to cause goitre in animals when administered to them for some weeks.

Goitre in animals and congenital goitre and cretinism in their offspring have been produced, under experimental conditions, by the administration to them of extracts of faecal material or of bacterial cultures made from faeces. Thus a watery filtered extract of faeces when administered to female rats throughout pregnancy as their sole source of drinking-water caused cretinism in some of their offspring. A similar but sterile extract made from the excreta and food residues accumulating in cages wherein rats were confined caused great increase in the rate of growth of embryonic thyroid tissue *in vitro* when added to the culture medium in high dilution (1 in 500,000); when present therein in greater concentration (1 in 5,000) it inhibited thyroid growth. This extract when given to rats living under conditions of perfect hygiene and fed on a well-constituted diet induced goitre in 8.3 per cent. of the animals. When an ill-constituted diet, capable, *per se*, of causing goitre in 39 per cent. of the animals, was substituted for the well-constituted one, this extract increased the incidence of the disease to 89 per cent., thus emphasizing the importance of the summation of goitrogenic influences. The goitrogenic action of insanitary conditions is counteracted by well-constituted diets containing adequate supplies of iodine.

INFECTIONS

As is well known the thyroid gland is very susceptible to stimulation by infections of various kinds. Its usual mode of response to them is an increased activity, characterized by epithelial hyperplasia, an increased production and output of the gland's hormone, and a greater or lesser disappearance of colloid from the organ. But according to Thomas (1935) the gland sometimes exhibits another mode of response. In this case the process of

secretion and storage of colloid may predominate over that of the excretion of hormone, and the histological features of the gland tend to approach those of diffuse colloid goitre. "If certain germs, like the bacillus of Koch, stimulate for a length of time the process of secretion [of colloid] in a dominant way, obliging the colloid to accumulate in the follicles and these to increase in size, we must admit a direct action on the thyroid; an action more or less specific on the part of certain microbes." This observation suggests an interesting possibility concerning the pathogenesis of goitre: "It becomes in these conditions extremely logical to look for the aetiology of colloid goitre, for example, in the action of a germ which, in the manner of the bacillus of Koch, stimulates [colloid] secretion in a predominant way but with a much more considerable intensity" (Thomas). In this connexion one may recall the experimental production of goitre in adult animals and of congenital goitre in their offspring by the oral administration to them of cultures of faecal bacteria and the curative effect of certain intestinal antiseptics (thymol, etc.) and of shock doses of vaccines in early cases of parenchymatous goitre in man (McCarrison, 1917).

Thomas's investigations have also thrown further light on the relation of intestinal toxæmia to the pathology of the thyroid gland—a relation the existence of which I have for many years maintained. He finds that intestinal toxæmia, surgically induced, has a profound action in at first stimulating the organ, but if long continued it induces pronounced atrophic and fibrotic changes.

Prophylaxis of Endemic Goitre

Within the last few years the value of iodine prophylaxis has been placed beyond question. The weekly administration to school children of tablets containing one milligramme of iodine has given excellent results in Switzerland. The efficacy of iodized kitchen salt, still under experimental investigation, opens up a wide range of possibilities of great promise. The dose of 0.5 gramme of potassium iodide to 100 kg. of salt appears sufficient, and is rarely followed by bad effects. But iodine prophylaxis has its limitations; always there is a residuum of goitre-incidence amounting to about 7 per cent. which it does not control (McCarrison and Madhava, 1932). Besides this specific means of preventing goitre it is essential to include in prophylactic measures the provision of a well-constituted diet containing all elements and complexes necessary for normal nutrition and to exclude all positive goitrogenic agents of whatever kind.

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J. Torgensen (*Norsk Mag. Laegevidensk.*, September, 1936, p. 951), who records two illustrative cases in children aged 8 and 9 years respectively, states that ischiopubic osteochondritis, which is an affection of the synchondrosis between the os pubis and ischium, was first described by Van Neck in 1925, and in greater detail by J. Heeren in 1933. It occurs in children in whom the synchondrosis is ossifying, and in several cases ossification is strikingly asymmetrical. The symptoms are pains in the lumbar region. X rays show a swelling of the synchondrosis, which is sclerotic at its margin and vacuolated in the centre. The condition probably predisposes to secondary infection.