STUDIES ON ENDEMIC AND EXPERIMENTAL GOITRE

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CONTENTS

I. Introduction

The subject-matter of this paper is a continuation of the researches on the subject of goitre carried out in this University (see papers by Hercus, Benson and Carter, 1925; Hercus and Roberts, 1927; Hercus, Aitken, Thomson and Cox, 1931; Hercus and Aitken, 1933). In the present paper the relation between lack of iodine and goitre is discussed, and the thesis that lack of iodine is the predominant factor in the production of endemic goitre is supported by the results of a survey of urinary excretion of iodine in certain New Zealand districts and in the islands of Samoa. The present position of goitre prophylaxis in New Zealand is reviewed and suggestions are advanced as to its further development. A further section presents the results of our recent researches on experimental goitre produced in laboratory animals.

II. Analytical method

The method previously described by Hercus and Aitken (1933) was modified in several respects to eliminate certain errors. The method of combustion previously used involved heating in an open crucible and was unsatisfactory in several ways. The organic material usually froths up and forms crusts of material that are not readily heated from below. An excessive temperature was therefore necessarily applied to that portion of the residue in contact with the crucible in an endeavour to char the material throughout. This heating was also unnecessarily prolonged or had to be repeated, while quite frequently portions of the material remained insufficiently heated and dark-coloured extracts were obtained. Also the free circulation of air over the heated residue promoted the volatilisation of iodide. The material was also liable to inflame or burn with uncontrollable incandescence, thus volatilising iodide. All these difficulties are overcome by heating the crucible inside a slightly larger crucible

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over a large Bunsen flame. As soon as all fuming has ceased the lid is applied. The flame is adjusted to reach just beyond the edge of the lid and adjustments made by experiment until, after 5 min. heating in a dark room, the lid shows a just visible red glow, and on lifting the lid the inner crucible is seen to be evenly heated to a dull red. This glow should not be visible in a lighted room—if so, the temperature is too high. By this means the material is heated as in a muffle and a much shorter time suffices to heat the material throughout. The incandescence which is liable to ensue in fibrous vegetable materials is also prevented, provided the precaution is taken of allowing the crucible to cool somewhat before removing the lid. Our experience shows that charring with exclusion of oxygen is sufficient to liberate the iodine in an extractable form.

Some authors, *e.g.* McClendon (1927), allege that the iodine is absorbed by carbon and cannot therefore be extracted with water. But potassium iodide in alkaline solution is not absorbed by carbon. Nevertheless, iodine does remain in the carbon after extraction. This is due to the fact that carbon, particularly when formed from soluble substances such as sugar or protein, forms waterproof protecting vesicles round particles of potash and potassium iodide. The carbonaceous residue requires to be finely ground with a little water. It is then taken up in 30 ml. water, evaporated to dryness, and reheated. After this treatment the alkali and the iodine can be extracted quantitatively if the mass be first boiled for at least 10 min. with 50 ml. of water before filtering and washed with liberal quantities of hot water.

Organic matter from three sources has been found to interfere with the titration: uncombusted matter from the sample, a resinous residue from the alcohol, and organic matter in the distilled water. The residue from the alcohol is due to polymerisation of traces of aldehyde by the action of the potash. The alcohol must therefore be purified by refluxing with 1 per cent. of potassium hydroxide followed by distillation in an all-glass apparatus. The distilled water required for the bromine oxidation and titration must be freed from organic matter by distillation from acid permanganate. This may not be necessary with all water supplies, but water distilled from the town water supply here contained volatile organic matter in quantity sufficient to cause serious error as the results of the tests given below show.

	Recovery	
Iodine taken	Ordinary distilled water	Water distilled from permanganate
$0{\cdot}5\gamma$	$0{\cdot}26\gamma = 52\,\%$	$0{\cdot}40\gamma = 80{\cdot}0\,\%$
$1{\cdot}0\gamma$	$0{\cdot}62\gamma = 62\,\%$	$0{\cdot}90\gamma = 90{\cdot}0\,\%$
$2{\cdot}0\gamma$	$1{\cdot}60\gamma = 80\,\%$	$1{\cdot}85\gamma = 92{\cdot}5\,\%$

In attempting to destroy organic matter by oxidation with chlorate, it was found that the addition of this substance to the estimation at the stage of the bromine oxidation greatly improved the recovery. Chlorate is stable on boiling in dilute sulphuric acid but appears to exert an oxidising action that prevents the reduction of the iodic acid by any trace of organic matter present.

In the cold the chlorate does not liberate iodine from iodide in dilute sulphuric acid with sufficient velocity to interfere with the titration and no positive error is introduced. We therefore take up the final evaporated alcohol extract with 2 c.c. of 0·1 per cent. potassium chlorate, add sulphuric acid and bromine and proceed in the usual way. We have used this method for a large number of estimations and are satisfied that by nullifying the effect of traces of organic matter it gives a better recovery without ever introducing a positive error.

After the work presented in this paper had been completed and this section of the paper prepared, the *Medical Research Council Report*, No. 201, on the "Determination of Iodine in Biological Substances" by C. O. Harvey has appeared. We propose in further work to follow the methods presented therein, as we consider it desirable that workers on iodine in biological substances should utilise a uniform and consistent method so that their results may be comparable. The methods that we have used, however, enable results to be obtained with a minimum of expensive apparatus and may still find a use where a suitable muffle furnace is not available.

III. Iodine in relation to goitre

Since Prévost (1830) put forward the theory that goitre was due to a lack of iodine, there has been much dispute about the rôle of iodine lack in the etiology of goitre. However, in recent times those workers (*e.g.* v. Fellenberg, Reith, McClendon and Lunde), who have made extensive investigations of the relation of iodine to goitre, agree in associating a high incidence of goitre with a low intake of iodine. The publications of Hercus *et al.* show that in New Zealand, too, goitre is associated with a low iodine intake. The data may be summarised thus: Where a high incidence of goitre exists a low intake of iodine is found; where a high intake of iodine exists goitre is absent or rare. From this arises the familar iodine "deficiency" theory (more correctly iodine-lack or iodine-insufficiency) which is rightly formulated thus: *A low intake of iodine is a prerequisite for high goitre incidence.* To make use of this theory we need to determine what amount of iodine is necessary to prevent goitre. To do this we need to determine the iodine intake not only in regions of differing goitre incidence but also in regions which may be regarded as non-goitrous. It is difficult or impracticable to determine the iodine intake directly with the necessary certainty because of

(1) The difficulty and uncertainty of the analysis of many foodstuffs except by McClendon's time-consuming tube method.

(2) The uncertainty of the composition of the diet.

(3) The large number of analyses which would be required.

We prefer, therefore, to base our conclusions on the more accurate determinations of urinary excretion which may be assumed to constitute some constant fraction of the intake.

In Table I are shown some data collected from the literature.

It will be seen that the highest excretion recorded for a goitre region is 87 micrograms (γ) per day recorded by Lunde. The lowest excretion for any area described by the authors as non-goitrous is 112γ per day recorded by v. Fellenberg. We may therefore state the iodine insufficiency theory in the following terms: *An iodine intake less than that which results in a daily urinary excretion of* 110γ *is a prerequisite for goitre production.* We may also deduce that a zero or only a slight goitre incidence is to be expected with intakes of iodine which result in daily urinary excretions between 90 and 110γ.

We have no exact data as to the proportion which the urinary excretion bears to the total intake of iodine which will allow us to transpose the above figures into daily intakes. Reith (1933) assumes that the urinary excretion is about 70 per cent. of the intake. On this basis the insufficiency theory becomes: *An iodine intake of less than* 160γ *per day is prerequisite for goitre production.* Similarly, intakes of 120–160γ will be associated with little or no goitre.

Table I. *Urinary excretion of iodine in relation to goitre*

	Daily urinary excretion		
	Goitrous region	Non-goitrous region	
Country	γ	γ	Authority
Switzerland	17–70	—	v. Fellenberg (1924)
Ligurian Coast	—	112	v. Fellenberg (1926)
Norway	28–87	173	Lunde (1928)
Holland	29–51	186	Josephus Jitta (1933)
Lettland	60–70	120–160	Kupzis (1932)
New Zealand	25–57	—	This paper, Table II
Samoa	—	146	This paper, Table II
Combined data	17–87	112–186	
	Average	151	

To complete this section of our knowledge of the etiology of goitre two things only are needed. The one is, the determination of urinary excretion in a large number of districts, both goitrous and non-goitrous, so that the gap between the 87γ per day of the highest goitrous and the 112γ per day of the lowest non-goitrous district may be bridged, and the other is an accurate determination of the proportion which the urinary excretion forms of the total intake. We will then be able to formulate the iodine insufficiency theory with final precision.

Is iodine deficiency the cause of goitre?

The iodine-deficiency theory is often stated in the form "Iodine deficiency is the cause of goitre". Since goitre, or at least endemic goitre, is always a sequel of a low iodine intake, it appears that this statement is true. It is incorrect, however, to suppose that iodine deficiency is the sole cause of goitre. Marine (1935) summarises some of the other factors which undoubtedly play rôles in the causation of goitre, viz. infections, high calcium intake, fat diets, meat diets, vitamin deficiencies, etc. There has appeared a large body of criticism of the iodine-deficiency theory not based on any determination of

iodine intake or environment. Much of this is merely the expression of personal prejudices following the tradition of the contemptuous treatment accorded Prévost's and Chatin's theories of the rôle of iodine. The remainder of the criticisms are based on the finding that some other factor plays a rôle in goitre causation. It is known to be quite fallacious to deny the operation of one cause of a phenomenon because another cause is found to operate. This fallacy, however, continues to engender and to maintain unnecessary controversy. The iodine-deficiency theory rests on positive findings which remain uncontroverted. Iodine deficiency is undoubtedly one of the causes of goitre. This statement, however, does not do justice to the pre-eminent position of iodine deficiency in the causation of goitre. A low intake of iodine is found in all goitrous districts. In other words, districts with high iodine intakes are always non-goitrous. This means that the other factors which have an effect on goitre incidence are only effective when the iodine intake is low. This pre-eminent rôle is best summarised by the statement that iodine deficiency is prerequisite for goitre production.

Another class of criticism of the iodine-deficiency theory is based on the deviations that have been found from an exact parallelism between the goitre incidence in a district and the extent of iodine deficiency indicated by iodine analysis. Hercus, Benson and Carter (1925) showed an inverse relation between goitre incidence and soil iodine in New Zealand. McClendon and Holdridge (1935) found an inverse relation between the incidence of goitre in recruits and the iodine content of foodstuffs in the state of Minnesota. Lunde (1928) found for Norway, and v. Fellenberg (1924) for Switzerland, an inverse relationship between the incidence of goitre in school children and the daily urinary iodine excretion. These findings furnish very conclusive evidence of the predominant position of iodine deficiency in the production of goitre. But authors who have collected and reviewed data from the literature have found considerable variation from a rigid inverse ratio and have accordingly repudiated or thrown doubt on the iodine-deficiency effect. The fallacy of such criticism is obvious. In the first place, it is for the most part impossible to make exact comparisons between different countries as to the intensity of goitre endemicity, particularly where the endemic is not sufficiently severe to produce a high incidence of such certain stigmata as cretinism and deaf mutism. There is no standard minimum enlargement above which the thyroid gland is to be regarded as goitrous. However elaborate may be our rules of classification, subjective and objective factors arise and affect the findings. The incidence fluctuates, moreover, according to age and sex, and unknown factors may affect it within an entire endemic region. There is also the difficulty referred to above of comparing with any degree of accuracy the iodine intakes in different countries. If our contention is accepted that with present methods the most satisfactory basis of comparison is the 24-hour iodine excretion in the urine the data available are extremely meagre. But even were reliable comparative data available it would be unreasonable to

expect to find a rigid inverse ratio to be demonstrated when so many variable factors influence the genesis of goitre in a community. The only way in which the iodine-deficiency theory as formulated above can be controverted is by the production of reliable evidence as to the existence of endemic goitre in a district where the average 24-hour iodine excretion in the urine is above 110γ, a level which our evidence suggests fixes the non-goitrous level.

Iodine and goitre in New Zealand

When Hercus, Benson and Carter (1925) found an inverse relationship between goitre incidence and soil iodine in New Zealand, there were certain anomalous districts. In particular, Taranaki showed a goitre incidence in excess of that predicted from the high iodine content of the soil. Shore and Andrew (1929, 1934) supported the iodine relationship in a close investigation of certain districts of North Island. There were anomalies in the Taranaki and Thames districts in that New Plymouth, the principal town of Taranaki, with soil iodine of 930 parts per 10 million, had approximately the same incidence as Thames with 74 parts per 10 million. We considered these anomalies to be explainable by variations in the availability of the soil iodine.

In 1933 Mecredy reported a goitre epidemic in the Taranaki district. Shore and Andrew (1934) confirmed the findings of Mecredy (1933) that a marked increase in the size of the thyroid glands of the school children of Taranaki had occurred and reinvestigated the iodine environment of this area in greater detail. They confirmed the previous soil analyses and reported a large number of analyses of milk, eggs, and vegetables. The figures showed extreme variations in successive determinations even on pooled milk samples in which a relatively stable iodine content would be expected. We are therefore unable to draw a definite conclusion about the iodine intake from these data.

It is to be regretted that these authors drew from these data the conclusion that no lack of iodine was operating at New Plymouth, implying that the iodine relation was not valid. We consider such a conclusion unwarranted. Before this could be done it would be necessary to determine accurately the intake of iodine in the region investigated, and to compare it with the value obtained similarly in a non-goitrous district.

We therefore decided to determine the daily urinary excretion of iodine in New Plymouth and the non-goitrous islands of Samoa. We also determined the excretion in the extremely endemic area around Cromwell in the Clutha Valley. For the purpose of this survey we analysed only 24-hour specimens, the total volume of which had been recorded. This was essential, as the iodine content of the urine passed varies at different times throughout the day. The results of the determination of 24-hour urinary excretion were as follows:

New Plymouth: 40, 51, 76, 43, 60, 68, 76, 71, 32, 51. Average 57γ.

Cromwell: 42, 20, 22, 10, 11, 16, 27, 28, 21, 20, 24, 41, 21, 20, 19, 51, 25. Average 25γ.

Samoa: 134, 183, 201, 168, 70, 134, 168, 112. Average 146γ.

The averages are given to the nearest whole number.

In Table II are shown the average iodine excretions for these districts along with the incidence of visible thyroid enlargement in school children and the iodine content of the soil.

It will be noted that the high iodine content of the New Plymouth soils is not reflected in the iodine excretion figures, thus supporting our belief that the iodine of these soils is in a relatively non-available form. On comparing the values obtained with those for other goitrous and non-goitrous districts as recorded in Table I, it is seen that the prevalence of goitre in Taranaki in no way conflicts with the iodine-deficiency theory.

Shore and Andrew (1934) drew the conclusion that "this cause (lack of iodine) obviously does not operate in New Plymouth". We have previously stated that such a conclusion was unwarranted; our results show that it is untenable. Plainly there is a lack of iodine in New Plymouth. The presence of goitre in this district with its high soil iodine was an exception to the earlier

Table II

District	Daily urinary iodine excretion γ	Percentage of goitre in school children	Soil iodine parts per 10 million
Cromwell	25	61	8·6
New Plymouth	57	(1928) 7	1005*
Samoa	146	0	281

* Shore and Andrew (1934).

hypothesis relating goitre to soil iodine. When, however, the iodine intake is investigated and compared with that of a non-goitrous district, this anomaly becomes the exception that proves the rule or at least supplies strong confirmatory evidence as to its validity.

We would contend, therefore, that the evidence that lack of iodine is the predominant factor in the causation of goitre in New Zealand is just as complete, convincing and unassailable as in the other parts of the world where it has been investigated.

The cause of the remarkable increase in the thyroid enlargements of school children in Taranaki remains unexplained. There is as yet no evidence that the adult population is experiencing the same phenomenon. It is well known that the incidence of goitre is subject to fluctuations in endemic districts and similar increases, the so-called "epidemics", have been recorded in many parts of the world. Bircher (1929) mentions a number of examples in Switzerland, Italy, Germany and France. Joll (1932) cites examples in England. The cause of these "epidemics" is as yet unknown. One fact, however, emerges—that they occur only in previously goitrous districts, and all the available evidence suggests that their occurrence is a clear indication for more effective iodine prophylaxis.

IV. GOITRE PROPHYLAXIS IN NEW ZEALAND

A brief review of the measures taken to prevent goitre in New Zealand may be of interest. Iodine has been advocated for goitre prophylaxis for some 15 years. From 1921 to 1926 tabloids of potassium iodide containing 0·065 g. were provided free by the School Medical Service to all children in endemic areas who elected to take them. The tabloids were given once weekly for three periods of 10 weeks throughout the year, and the participating children were kept under medical observation for any evidence of possible ill effects. In 1925 12,000 children were receiving the tabloids. The results, both prophylactic and therapeutic, were most gratifying, and no untoward effects were observed. With the legal sanction for the importation of iodised salt into the country in 1925, this method of prophylaxis was gradually given up, as it was felt that iodised salt was the more physiological method of supplementation besides being applicable to the whole population. The school prophylaxis served, however, the useful function of drawing the attention of a large section of the community to the goitre problem and of accustoming them to the conception that prevention was feasible. It also served to demonstrate that relatively large doses of iodine, 0·065 g. or 65,000γ, can be exhibited at weekly intervals for relatively long periods to children, many with considerably enlarged thyroid glands, with nothing but beneficial results.

General prophylaxis with iodised salt

Iodised salt was first used in New Zealand for goitre prevention in 1923, when salt iodised so as to contain 100γ per g. was introduced for all domestic purposes to the dietary of an orphanage in Dunedin. The children were kept under close observation for 18 months, and the results recorded by Hercus, Benson and Carter (1925) were most encouraging and prepared the way for the entry of commercial iodised salt into New Zealand. In February 1924 the New Zealand Branch of the British Medical Association, at their annual meeting, urged the Government to introduce iodised salt into all endemic areas. They suggested that all domestic salt sold in these areas should contain 1 part of potassium iodide to 200,000 parts of salt. They considered that this prophylactic measure was of sufficient importance to warrant a measure of compulsion in its introduction. The Government was impressed by the representation and agreed to insert into the regulations under the Sale of Food and Drugs Act, 1908, a definition of iodised salt prescribing the permissible addition of iodine as 1 part of potassium or sodium iodide per 250,000 parts of salt. It was not considered reasonable to adopt the suggestion that all domestic salt in endemic areas should conform to this standard. While the regulation marked a considerable step forward by enabling iodised salt to be sold commercially, the labelling restrictions which the regulations imposed insisting that iodised salt could only be sold in packages on which the word "Iodised" was written in capital letters of prescribed size, definitely restricted its use. People could

get iodised salt only by asking specifically for it, and the iodisation of the ordinary "loose" salt of commerce was illegal. These regulations came into force in June 1924, and before the end of that year iodised salt conforming to the regulations was available in cartons and 2·2 kg. bags throughout New Zealand. By January 1927 enquiries made from grocers in Christchurch and Timaru—the two principal centres of population in the endemic district of Canterbury—illustrated the fact that approximately 5 per cent. of all domestic salt sold was iodised, and that it was principally sold in cartons for table use.

At the Australasian Medical Congress held in Dunedin in February 1927 the whole subject of goitre in New Zealand was reviewed. The conference was sufficiently impressed with the urgency of the situation to pass a resolution urging the Government and the medical profession to increased activity in their efforts to secure the general use of iodised salt. In the light of evidence brought before the Congress which suggested that the incidence of toxic goitre in endemic areas was on the increase as the result of the indiscriminate use of iodine in proprietary goitre remedies, a further resolution was passed asking the Government to take steps to make the sale of proprietary goitre remedies illegal except by chemists on the prescription of a doctor. Both of these resolutions bore fruit; the first had some effect in stimulating the demand of the public for iodised salt for all domestic purposes, and the latter led to an endeavour by the Government to protect the public from the advertising of proprietary goitre remedies. Considerable legal difficulties confronted the Government in the latter problem, and the most that could be done was to introduce into the regulations under the Sale of Food and Drugs Act a clause prohibiting the advertising of any substance as suitable for the prevention, alleviation, or cure of goitre unless the amount of iodine was stated and the words "Danger. This preparation should not be used except under medical direction" were displayed on the label. Although this regulation has prevented the advertising of goitre remedies, it has also raised a legal barrier to the advertising of iodised salt as a goitre remedy without the addition of the cautionary legend, and it has similarly prevented the fishmonger or grocer from advertising that kelp salmon, or oysters, or other sea foods are of value in the prevention of goitre. Subsequent Government action with regard to iodised salt has been confined to:

(*a*) In April 1931 permitting by arrangement the use of iodised salt in butter. Few dairy factories, however, have taken advantage of this sanction.

(*b*) In May 1932 amending the original standard of iodised salt in order to define maximal and minimal contents of iodine. The definition now in force states that iodised salt must contain not more than 2 parts nor less than 1 part of sodium or potassium iodide per 250,000.

In February 1935, at the Annual Conference of the British Medical Association in Dunedin, the situation again came under review, and the conference once more passed a resolution urging the Government to reconsider the original proposals made in 1924 suggesting that all salt used for domestic purposes

should be iodised and should be known as standard salt, and that the Government and the medical profession should take immediate steps to increase the use of this salt throughout the Dominion. The result of this action is not yet evident.

Results

In endeavouring to assess the results of this measure two questions at once arise; to what extent has iodised salt been adopted by the people generally and what demonstrable effect has it produced in the prevention of goitre?

Utilisation of iodised salt.

Before the utilisation of iodised salt can be determined, it is essential to know the average salt consumption of the community. In a previous communication (Hercus and Roberts, 1927) we estimated the domestic consumption in New Zealand at 6 g. exclusive of salt used in bread, dairy products and meat. We have verified this figure from carefully controlled estimations in a number of institutions and private houses. The amount of salt consumed in bread, dairy products and salted meats we estimate to be approximately 5 g. per day, making a total consumption of 11 g. of salt which is used to supplement the salt of the food. It is evident that striking differences occur in the consumption of salt in various countries. Muggia (1929) states that the average daily consumption of salt in the province of Valtellina in Italy for all purposes including bread, dairy products and sausage manufacture is 20 g. Silberschmidt (1929) gives figures that indicate that in Switzerland the consumption is 24·5 g. per day. Habit and the nature of the diet play an important part in salt requirements, and the New Zealand diet, with a higher meat content than in Italy or Switzerland (207 lb. per head per year), requires less salt supplementation. The significance of this fact is obvious when salt is to be the medium by which iodine supplementation is to be carried out. It will be discussed in a subsequent paragraph.

It is fortunate that the New Zealand Customs Department has kept records as to the importation of iodised salt from 1927 to 1934 inclusive. Table III shows the estimated population of New Zealand for each year of this period, the amount of the importation, and the calculated daily consumption per head assuming the salt to be evenly distributed.

It will be seen that though with the exception of the year 1932 each year shows an increased consumption, in 1934 iodised salt constituted approximately 30 per cent. of the average total daily domestic consumption of salt. This result cannot be regarded with satisfaction by the advocates of voluntary prophylaxis. It is true that an analysis of the importation by district shows considerable variation and that the districts of Canterbury and Otago are importing proportionately more iodised salt than other districts. The proportion of iodised salt, however, remains unduly low even in these areas.

It is instructive to contrast this finding with the experience of other countries in goitre prophylaxis by voluntary means. Dieudonné (1929) states

that in Bavaria in the district of Kempton 88 per cent. of the community were using iodised salt voluntarily within 3 years of its introduction. Wagner-Jauregg (1929) states that within $3\frac{1}{2}$ years of the introduction on a voluntary basis of iodised salt into Vienna 47 per cent. of the salt consumed was iodised. McClure (1934) states that iodised salt containing 0·01 per cent. of sodium iodide was introduced in 1924 in Michigan through the grocery stores without any legislative action, and that by 1933 the ratio of iodised to non-iodised salt for domestic consumption was 8 to 1. It is noteworthy that while in the beginning the use of iodised salt was a purely voluntary matter in Switzerland and the hope was cherished that by means of intensive propaganda it would be possible to persuade the whole population to use it, a measure of compulsion has been found necessary in at least six cantons. In Italy in the province of Valtellina compulsion or what is termed the "tacit" introduction of the measure was adopted from the outset.

Table III

Year	Population of New Zealand	Importation of iodised salt in kg.	Grams per head per year	Grams per head per day
1927	1,437,980	244,973·03	172·36	0·47
1928	1,453,517	509,403·68	349·27	0·95
1929	1,470,654	587,589·81	399·16	1·09
1930	1,488,595	725,215·68	485·35	1·32
1931	1,510,940	787,347·99	521·64	1·42
1932	1,524,633	733,090·17	480·81	1·31
1933	1,536,964	980,195·94	639·57	1·75
1934	1,548,909	1,034,454·75	666·79	1·82

The slowness with which the New Zealand public has adopted the measure can probably be ascribed partly to the less intense nature of the endemic in this country, partly to the less active propaganda which has been carried out, and partly to the Government regulations which restrict the free use of iodised salt in commerce. Economic considerations can play no part, as the difference in cost over an average of 7 years in an institution of 1356 persons amounted to £1. 13*s*. 0*d*. There is also no conflict of opinion as to the value and harmlessness of the procedure. Amidst the clash of opinion as to the causation of goitre at the last International Conference in Berne, no voice was raised against goitre prophylaxis by iodised salt.

Effects of goitre incidence.

With an iodised salt utilisation of 30 per cent. of the total domestic consumption of salt, little effect would be expected in the general community. In countries where the adoption of iodised salt has been more general, definite results have been forthcoming within a few years. McClure (1934) records that in Michigan by 1932 the incidence of goitre in school children had fallen from 35 to 1 per cent., the amount of goitre surgery had fallen by 60 per cent., and the annual death-rate from goitre had fallen from 4 to 3 per 100,000. No cases of hyperthyroidism were traced to the use of the salt. Wagner-Jauregg (1929) records similar results in various European countries. Nothing com-

parable has occurred in New Zealand as a whole. In the school children there is little variation in incidence. In Taranaki a notable increased incidence continues to be observed. There has been an increase in goitre surgery as measured by the admissions to public hospitals; thus, 386 persons were admitted for simple goitre in 1933, 507 in 1934. Death-rates for diseases of the thyroid show no decrease but remain relatively high.

If districts where iodised salt is in more general use are studied, the results are still disappointing. The *Annual Reports* of the School Medical Officers of Canterbury and Otago (1934, 1935) give conflicting results. In 1935 Dr Abbott of Otago states: "In spite of the fairly general use of iodised salt, there appears from the year's figures to be a decided increase in the amount of goitre in all ages in both incipient and small classes." Dr Stevenson of Otago concludes, "that though prophylactic measures have a value, there is some more complex factor complicating the incidence suggesting hereditary influences". Drs McClaglan and Phillips of Canterbury find, "that there is a definitely lower incidence of goitre in pupils using iodised salt". Our own observations in various institutions and private homes extending over a period of 10 years are in keeping with those of the Canterbury observers. Where iodised salt has been in regular use for table purposes alone there has been no prophylactic effect which is to be expected as the average amount consumed per day by this method as estimated in the University Domestic Science Hostel is only 1·5 g. Where the salt has been in regular use for periods over 2 years for all domestic purposes there is a definitely prophylactic effect and some therapeutic action. Several cases of thyroid enlargement have occurred, however, in persons in whom previously the thyroid gland appeared normal. Thus, in the Dunedin Nurses' Home which has used iodised salt for all domestic purposes since 1926, two nurses out of a staff of 70 have developed small goitres. A few cases of goitre have presented themselves at the Goitre Clinic of the Dunedin Hospital that have developed goitre in spite of regular prophylaxis. These cases have been confined to adolescent girls and pregnant women. Of particular interest is the case of two European girls from Samoa who developed thyroid enlargement within 2 years of residence in Dunedin in spite of a fairly regular use of iodised salt. Sufficient evidence is available therefore to show that the regular use of iodised salt of the present New Zealand standard for domestic purposes is not an efficient protection against goitre. It is not until the results from the Sunnyside Mental Hospital of Christchurch which has since 1926 used iodised salt for all purposes—in bread making, dairy products, etc. in addition to domestic use—are considered that results comparable to those of Europe can be claimed. The prophylactic and therapeutic results have been excellent. No person has developed goitre within the institution, though prior to 1926 50–60 per cent. developed goitre within 2 years. The therapeutic value of the measure has been manifest among several hundreds of persons with large goitres, and no ill effects have been observed. This result can only be ascribed to the much larger daily consumption of iodised salt.

Future requirements

These inconclusive findings contrasting so unfavourably with the experience of other countries can be simply explained. There is no need to throw dubiety on the prophylactic value of physiological quantities of iodine nor to postulate the operation of unknown factors. Two main facts emerge. The utilisation of iodised salt by the community is totally inadequate, and the standard of iodine in the salt is too low to be effective. As no part of New Zealand so far investigated can safely dispense with iodine supplementation a domestic consumption of 30 per cent. must be regarded as unsatisfactory. The whole population should be using it preferably for all domestic use and in bread and dairy products. To secure this end as speedily as possible the present legal position of iodised salt requires to be completely reversed. Iodised salt should be regarded as the standard salt of the country, and all restrictive legislation which in any way hampers its utilisation should be removed. Non-iodised salt could still be on sale but only if sold in packages with the label "Non-Iodised" attached, and, to make the reversal complete, the addition of the caption "Dangerous, the use of this salt exposes the user to the risk of goitre".

The clinical evidence indicates that even where the salt has been used regularly for table and cooking purposes the results fall short of expectations. The iodine intake required to eliminate the risk of endemic goitre in a community is apparently between 120 and 160γ per day. The intake in Samoa calculated from the urinary excretion figures in Table II, however, is as high as 208γ. The intake in New Zealand without supplementation varies from 36γ in Cromwell to 81γ in New Plymouth. The required supplementation we would suggest for New Zealand as a whole should be in the region of 100γ. It is evident that 6 g. of salt cannot supply this amount if conforming to present standards. The most that could be supplied if the salt contained 2 parts per 250,000 is 36γ. It should be noted that many samples of salt analysed from routine samples of iodised salt in the market fell below the standard and some have been as low as 0·2 part per 250,000, which would supply only 3·6γ. To demonstrate the inadequacy of the supplementation we determined the daily urinary excretion in the Dunedin Nurses' Home where 5·3 g. of iodised salt are used for domestic purposes and compared it with a control group of nurses not using iodised salt. The iodised salt was calculated to supply a supplementation of approximately 25γ which should increase the urinary excretion by 17·5γ. The findings were as follows:

Control group: 38, 36, 35, 42. Average 38γ.
Iodised salt group: 42, 52, 55, 43, 90, 57. Average 57γ.

The difference in average excretion is 19γ, which is in good agreement with the calculated figure and confirms the inadequacy of the supplementation.

To supply 100γ in salt used for table and cooking purposes alone necessitates in New Zealand that 6 g. of salt must contain this amount which means that the salt must contain 5–6 parts per 250,000. If iodised salt is in addition

to be used for bread, dairy products and other salted foods, then 11 g. of salt will carry the 100γ which will mean a standard of 3–4 parts per 150,000. It is immaterial which method is used, although we favour the latter method as being perhaps more certain in application.

If this measure is adopted it is our firm belief that New Zealand can stage a successful large-scale demonstration of effective goitre prophylaxis.

V. EXPERIMENTAL GOITRE

Chesney, Clawson and Webster (1928) first reported the occurrence in cabbage of an active goitrogenic agent which could be demonstrated by feeding to rabbits. Webster and Chesney (1930) reported further studies on this goitrogenic agent, and described the thyroid enlargement obtained as a diffuse parenchymatous goitre. The goitrogenic activity of cabbage was confirmed in India by McCarrison (1930–31), and in England by Spence, Walker and Scowen (1933). The latter reported the presence of anti-goitrogenic factors in hay and in whole oats, which they considered to be responsible for negative results in some of their experiments. Webster, Marine and Cipra (1931) reported a seasonal variation in activity, winter cabbage being more active than summer cabbage. There was also a geographic variation, and a variation of activity in successive years.

In a test of New Zealand cabbage in the winter of 1931 we found only a slight activity (Hercus and Aitken, 1933). Our aim was the production of large goitres several grams in weight. This result was not attained, the average weight of the glands being 0·55 g. Continuing the work we attempted a survey of a wider scope than in our first test. The rabbits used were males, 3 months of age, and confined either singly or in pairs in steel cages.

To evaluate the possible effect of anti-goitrogenic factors which we thought might be responsible for the slightness of the activity found, we maintained rabbits on cabbage alone, cabbage with oats, cabbage with hay, and on hay, oats and water for times up to one year. We confirmed Spence, Walker, and Scowen's (1933) finding that rabbits do not do well on cabbage alone. Such rabbits ate increasing amounts of cabbage up to 500 g. per day but became emaciated and eventually died. Nothing of importance was found post mortem.

In order to detect geographic variations, rabbits bred in the laboratory were sent to three goitrous districts at some distance and maintained there on a cabbage diet. At the termination of the experiment the animals were returned to the laboratory for examination.

Any marked annual variation of activity would also have been detected as the experiments were in progress for 3 years (1932–4).

The results are tabulated in Table IV. Since the different cabbage diets did not lead to any different result they are not recorded separately in the table. The animals are arranged in the order of increasing duration of experiment since it was expected that the glands would show a progressive enlargement.

It appears from the weights of the glands that there was never any marked activity. In Chesney, Clawson and Webster's (1928) original communication the average weight of glands after 41–60 days of feeding was 0·86 g. and with 81–100 days' feeding and all longer times the average weight was over 1 g. The largest gland recorded by them weighed 43 g. We therefore felt that we could not ascribe marked activity to any sample of cabbage which did not produce in 60 days glands of an average weight in excess of 0·5 g., while in longer experiments we expected glands in excess of 1 g. in weight.

Animals 14, 15 and 20 indicate that in 1932 there was a moderate activity greater than that in succeeding years.

Table IV

No.	Locality of exp.	Beginning of exp.	Duration days	Weight of thyroid g.	Histology
		(*a*) Cabbage diets			
1	Dunedin	May 1934	60	0·340	+ +
2	,,	May 1934	60	0·295	+ +
3	Ashburton	Aug. 1933	60	0·093	+
4	,,	Aug. 1933	60	0·175	+ +
5	Dunedin	Aug. 1933	80	0·195	+
6	,,	Aug. 1933	80	0·280	+
7	Pembroke	Aug. 1933	80	0·123	+ +
8	,,	Aug. 1933	80	0·105	+ +
9	Stratford	Aug. 1933	80	0·167	0
10	,,	Aug. 1933	80	0·157	0
11	,,	Aug. 1933	80	0·180	0
12	,,	Nov. 1933	120	0·190	0
13	,,	Nov. 1933	120	0·135	0
14	Dunedin	July 1932	180	0·590	+ + +
15	,,	July 1932	180	0·670	+ + +
16	,,	Jan. 1934	180	0·230	+ +
17	,,	Jan. 1934	180	0·420	+ +
18	,,	Jan. 1934	180	0·235	+ +
19	,,	May 1934	180	0·325	+ +
20	,,	July 1932	360	0·615	+ +
		(*b*) Hay, oats and water			
21	Dunedin	Aug. 1933	270	0·315	+ + +
22	,,	Aug. 1933	330	0·440	+ + +
23	,,	Aug. 1933	330	0·385	+ + +
24	,,	Aug. 1933	330	0·410	+ + +

Animals 21, 22, 23 and 24 are interesting in that they show that a diet of hay, oats and water was not without effect on the thyroid, the glands being about twice normal size. Histologically there was in these glands a more intense hyperplasia than in the animals on cabbage, the appearance corresponding exactly with that figured by Chesney, Clawson and Webster (1928) or by Webster (1932). This result is opposed to the finding of Baumann, Webster and Marine (1929), who state that hay and oats did not lead to enlargement, and to that of Spence, Walker and Scowen (1933) who under certain circumstances found for these substances an antigoitrogenic property. This discrepancy is possibly the result of differences in iodine content.

As a result of this phenomenon all rabbits at Dunedin that have reached the age of 6 months or more have shown hyperplastic thyroids with enlargements up to twice normal, and we are in consequence unable, except for the

year 1932, to ascribe any activity to New Zealand cabbage, since any effect observed may be explainable by the low iodine content of the environment.

In seeking some other means of producing experimental goitre we turned our attention to the outbreaks of congenital goitre that appear in domestic animals in New Zealand. Such outbreaks occur frequently in areas where the incidence of goitre in man is high. These areas are found typically in the great river valleys and flood plains of the South Island, of which the Clutha Valley is a typical example. The Clutha river, rising in the snow-fed lakes of Wanaka, Hawea and Wakatipu, flows for some 210 miles through gorges alternating with open valley and river flat to the sea. Goitre is extremely prevalent in man and animals throughout the whole course of the river, and during the last 30 years sporadic outbreaks of congenital goitre in lambs have occurred. Hopkirk and Dayus (1930) describe a typical outbreak in the Lake Wanaka district in which 100 goitrous lambs, some showing hairlessness and other evidences of iodine deficiency, were born in a flock of 1100 cross-bred ewes. The ewes had been pastured for some 2 years on alluvial flats upon which were growing English grass and clover, their rations being supplemented during the winter with turnips and clover hay. The lambs from a flock of 300 ewes which had been on the same pasture and received the same supplementary feeding but had only been brought in from the adjacent mountains for 1 year were unaffected. The thyroids of the affected lambs were large, up to 202 g. in weight, and the iodine content per gram was extremely low. Three soil samples gave an iodine content of 6, 15 and 7 parts in 10 million, which is a low figure. It will be noted that the dietary supplementation included turnips which are in the same genus of the Cruciferae as cabbage. As it has been our experience that these outbreaks have been invariably associated with the feeding of turnips to the effected flocks during the winter months, we determined to investigate whether turnip contained a goitrogenic factor.

Turnip from three sources was tested. Of these the Dunedin district is moderately goitrous though without history of congenital goitre in stock. The Mt Burke and Glendhu stations are in the Clutha Valley district where outbreaks of congenital goitre have occurred. For the purpose of the tests male rabbits of 3 months age from the laboratory stock were used. The diets consisted of turnip roots *ad lib.* with supplements of hay and rolled oats. The results are shown in Table V.

It will be seen that the only positive result was in the Mt Burke 1933 experiment, in which rabbits were sent from the laboratory stock to be fed at Mt Burke and returned at the termination of the experiment. In 1934 turnip from Mt Burke was tested in the laboratory but proved inactive. We consider the difference to be due to the absence of activity from the 1934 turnip and not to the change of environment. The activity shown in 1933 when glands of over 1 g. in weight were produced in 60 days was approximately as great as that recorded by Chesney, Clawson and Webster (1928) for the most active samples of cabbage.

Besides the leaves of cabbage (*Brassica oleracea*) the leaves of some other Brassicae have been tested with positive results. Webster (1932) reports that Brussels sprouts and cauliflower were active, while Stiner (1933) found that kohl-rabi leaves (*Brassica oleracea* var. *gongiloides*) were active when tested on guinea-pigs. As far as we are aware, our result is the first demonstration of activity in the roots of a *Brassica* species.

We consider it likely that the sporadic goitrogenic activity of turnip roots would contribute to the production of goitre epidemics in stock.

Since we were unable to obtain active samples of turnip at the laboratory we turned to other substances. From a consideration of the stability of the active agent which is destroyed by drying the cabbage but not by steaming we had at first supposed that the activity might be due to highly unsaturated

Table V. *Results of turnip-feeding experiments*

No.	Place of exp.	Date of exp.	Source of turnip	Duration of exp. days	Wt. of gland (g.)	Iodine content of gland, γ per g. dry wt.	Histology	Result of exp.
1	Dunedin	April 1933	Dunedin	90	0·250	0·26	+	Negative
2	,,	April 1933	,,	90	0·202	0·31	+	,,
3	,,	May 1934	,,	60	0·195	0·72	+	,,
4	,,	May 1934	,,	60	0·190	0·68	+	,,
5	,,	May 1934	,,	60	0·230	0·47	+	,,
6	,,	May 1934	,,	60	0·205	0·43	+	,,
7	,,	June 1934	Mt Burke	60	0·140	1·20	+	,,
8	,,	June 1934	,,	69	0·200	0·76	+	,,
9	,,	June 1934	,,	60	0·215	0·58	+	,,
10	,,	June 1934	,,	60	0·185	0·61	+	,,
11	Mt Burke	Aug. 1933	,,	60	1·013	0·08	+ + +	Positive
12	,,	Aug. 1933	,,	60	1·050	0·07	+ + +	,,
13	Glendhu	April 1934	Glendhu	60	0·190	0·83	0	Negative
14	,,	April 1934	,,	60	0·290	0·41	+	,,

"drying" oils. This would have accounted for Baumann, Cipra and Marine (1931) finding the activity in the ether-soluble extract of cabbage. However, we were unable to maintain this hypothesis since unsaturated oils which we tested showed little or no effect, while also it could not account for the inactivity of our own cabbage. We therefore concluded that the activity was due to a glucoside or glucosides which are destroyed by enzyme action when the cabbage is dried. Presumably after steaming, which would destroy the enzymes, the cabbage could be dried without loss of activity. We are not aware of this experiment having been performed and we are unable to test it ourselves because of the lack of active material.

On the assumption that the activity was due to glucosides we were led to test the activity of the seeds of various Brassicae, since seeds are in general relatively rich in glucosides. For the tests young male rats of 50–60 g. weight were used. In early experiments positive results were obtained but were com-

plicated by vitamin and other deficiencies. The diets used in subsequent work consisted of:

Ground seed	... ...	50
Skim-milk powder	...	30
Maize meal	... ...	19
Sodium chloride	...	1
		100

In addition each rat received 0·1 ml. of cod-liver oil and 0·1 g. of marmite incorporated in the diet.

The seeds were finely ground in a coffee mill. Where so indicated the ground seed was steamed for half an hour in a shallow layer in an Arnold steriliser before incorporation into the diet. The control diet was the stock laboratory diet of the following composition:

Bran	... ...	5 parts
Pollard	... ...	5 ,,
Meat meal	...	2 ,,
Maize meal	...	2 ,,
Bone meal	...	2 ,,

In addition oats and kibbled maize are given on alternate days.

In each test six rats were used and the feeding was continued for 30 days. At the termination of the experiment the rats were killed with coal gas. The appearance of the glands was noted and after dissection the glands were weighed. In each group one-half of the glands were submitted to histological examination and the others used for iodine estimation. The results are summarised in Table VI.

Table VI

Diet	Average thyroid weight g.	Total iodine per gland mg.	Iodine content mg. per g. fresh weight	Histology
(*a*) Inactive:				
Control	0·009	0·0042	0·47	Normal
Wheat	0·013	0·0047	0·36	,,
Steamed rape seed	0·008	0·0048	0·60	,,
(*b*) Active:				
Steamed black mustard*	0·011	0·0005	0·045	Hyperplastic, no colloid
Steamed white mustard	0·024	0·0008	0·033	,,
Unsteamed rape seed	0·022	0·0007	0·032	,,
Unsteamed cabbage seed	0·025	0·0007	0·028	,,

* Classed as active on basis of histology and iodine content although it did not cause enlargement.

With the exception of the cabbage seed and steamed black mustard which are the results of single experiments the tests have been repeated with similar results.

The histology of those glands classed as normal was characterised by areas of colloid storage. There is always considerable variation throughout any

section, hyperplastic areas occurring amidst areas of colloid storage. In the active glands the appearance was uniform throughout with very little or no colloid, the epithelium being heightened and proliferated so as to fill the lumina of the acini.

The naked eye appearance of the colloid-containing glands was characteristic, being of an inconspicuous orange pink colour. The hyperplastic glands were a conspicuous deep red, so that the difference in naked eye appearance before the glands were dissected out was more striking than the relative weights would suggest.

The iodine contents are what would be expected from the histology of the glands, lack of colloid being reflected in a low iodine content.

Of those diets classed as inactive the wheat diet was originally included as a control for the other seeds. As it seemed uniformly to give larger glands than the stock diet, its use for this purpose was unsatisfactory.

Of those substances classed as active the steamed black mustard behaved anomalously in that in the single experiment in which it was tested it produced a histological activity comparable with that produced by the other active substances but without any marked increase in the size of the gland. The other active substances produced equivalent increases in size of the gland —2½–3 times normal—and the same extreme histological activity. The result obtained with the black mustard may be explainable by a lower degree of goitrogenic activity which had caused depletion of the colloid of the gland by the end of the experiment but would have required further time to produce a marked enlargement.

The most interesting results are those obtained with rape seed, steamed and unsteamed. Webster (1932) recorded that steaming enhanced the activity of active samples of cabbage and we were prepared for a similar effect. The result, however, is quite the reverse—steaming has removed all detectable activity. This result has been obtained in three separate parallel experiments at different times and with two different sources of rape seed. It appears at first consideration that the activity of the Brassicae seeds is of a different kind from that of cabbage. If, indeed, the activity is in each case due to glucosides it appears that in rape seed the enzymes are essential to the development of activity while in cabbage they are not essential. Unfortunately we cannot test the effect of unsteamed white mustard as, except the enzymes be destroyed, the addition of any considerable quantity of this substance to the diet renders it unpalatable through the liberation of the mustard oil. The effect of steaming on the activity of cabbage seed which we are at present testing will be enlightening, as it will show whether the seed of the cabbage behaves in the same way as the leaves. Other work in progress includes the further survey of the Brassicae seeds with the rat as a test animal and also the effect on the rabbit of those substances found active for the rat.

On analogy with rabbit experiments we expected a progressive enlargement with increased duration of experiment. We therefore put a number of

animals on the unsteamed rape-seed diet and sacrificed animals at 2, 4, 6 and 8 weeks. The result is shown in Table VII.

As shown in the table, there was no progressive increase in size of thyroid after 4 weeks. After this time involution and colloid storage began, and at 8 weeks the glands were pale in colour and histologically of the colloid storage type. It appears that we have here the hyperplasia-involution cycle put forward by Marine (1935) as the mechanism of production of simple goitre. The behaviour here is quite different from that in rabbits in which the hyperplasia is progressive and no colloid goitres appear during cabbage feeding. The difference may be due to the different response of the two animals.

Table VII

	2 weeks	4 weeks	6 weeks	8 weeks
Weight of thyroid	0·010	0·021 g.	0·024 g.	0·024 g.
Total iodine	0·0017 mg.	0·0085 mg.	0·0025 mg.	0·0060 mg.
Iodine mg. per g. fresh weight	0·17	0·04	0·10	0·25
Histology	Moderate hyperplasia reduced colloid	Intense hyperplasia loss of colloid	Beginning involution	Colloid storage

These results, together with the positive results obtained with turnip roots in rabbits, show that the goitrogenic properties of *Brassica* species are not confined to the leaves but are probably demonstrable in all the tissues of these plants.

VI. SUMMARY

1. Some improvements in the determination of small quantities of iodine in biological substances are described.

2. The thesis that a low iodine intake is prerequisite for goitre production is supported.

3. A survey of determinations by various authors of the daily urinary iodine excretion in goitrous and non-goitrous regions leads to the conclusion that the critical level of iodine intake sufficient to suppress goitre is between 120 and 160γ per day.

4. Determinations of urinary iodine excretion in New Zealand and in the non-goitrous islands of Samoa are presented which show that in the parts of New Zealand investigated the iodine intake is at a low or goitrous level.

5. The result in New Plymouth, Taranaki, shows that a high content of iodine in the soil does not necessarily assure an adequate iodine intake.

6. The progress of prophylaxis by iodised salt in New Zealand is reviewed, and from consumption data it is concluded that iodised salt constitutes approximately only 30 per cent. of the domestic salt consumption of New Zealand.

7. To ensure a more general use of iodised salt it is recommended that the regulations be amended to provide that:

(*a*) Ordinary domestic salt shall be iodised.

(*b*) Non-iodised salt shall be sold only in packages labelled "Non-iodised" and with the addition "The use of this salt exposes the user to the risk of developing goitre".

8. The results obtained hitherto with the use of iodised salt are briefly reviewed and attention drawn to some apparent failures even when iodised salt has been used for all domestic purposes. These failures are attributed to the standard for iodised salt being too low.

9. It is concluded that for New Zealand a supplementation of at least 100γ per day is necessary to afford complete protection against goitre.

10. To provide the necessary amount of supplementation the iodine content of iodised salt in New Zealand requires to be raised. We recommend therefore that either

(*a*) If the domestic salt only is to be iodised the standard be fixed at from 5 to 6 parts of potassium iodide (KI) per 250,000 of salt, or

(*b*) If iodised salt is to be used in the manufacture of bread, butter, bacon and other salted foods, the standard be fixed at from 3 to 4 parts of potassium iodide (KI) per 250,000 of salt.

11. In New Zealand cabbage has not shown any marked goitrogenic activity as tested on rabbits.

12. Turnip roots showed sporadically a goitrogenic activity comparable with that found for the most active samples of cabbage in other countries.

13. In tests of *Brassica* seeds on rats, goitrogenic activity was found in rape seed, cabbage seed, steamed white mustard seed, and steamed black mustard seed.

14. The activity of rape seed was destroyed by steaming.

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