

S T U D I E S   O N   G O I T R E

I N   N E W   Z E A L A N D .

by

A . M . D R E N N A N , M . B . , Ch . B .

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STUDIES ON GOITRE IN NEW ZEALAND .

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## I. INTRODUCTION.

Some explanation, nay even apology, is necessary to account for the presentation of still more work on the much laboured subject of Goitre.

My interest in the subject was aroused shortly after my arrival in Dunedin, New Zealand, early in 1917, by noticing the obvious fact that a large proportion of the young women presented thyroid enlargement. This could be observed any day by the simple procedure of walking along the streets and noticing the necks - amply displayed as is the modern fashion - of the female population. It appeared to me that either I had been unobservant in the Old Country or that I was noticing something to me new and unusual. I enquired of my colleagues, particularly my new clinical colleagues, and several said they had not especially noticed this prevalence of prominent thyroids, others remarked that most of the enlargements were purely physiological and of no moment. However, it appeared to me, without then actually estimating the percentage, that the number of specimens of goitre coming to the laboratory - after I had asked that all removed be sent - was greater, proportionally, than what I recollected as occurring in the Pathological Department of the Royal Infirmary, Edinburgh. This might still have been a coincidence, or due to more frequent operative measures than formerly, but it left the impression, strengthened by my peripatetic observations that goitre was relatively common here.

The mortality returns were next consulted but all the information obtainable from these, at that time, was that, under

Goitre, an occasional fatal case of exophthalmic goitre was recorded.

The returns by the Defence Department of rejections of recruits from Class "A", from 1916 to 1918, furnished interesting information; but, as no other source of enlightenment as to the prevalence of this condition, particularly among females, seemed available I suggested to the Health Department, about 1919, that data as to goitre were desirable and it might be instructive to make it notifiable. This was accordingly done in 1920, notification of goitre being put on a voluntary basis.

As far as accurate statistics of frequency go this notification procedure was a failure, but it served to support the suggestion that goitre was a prevalent condition in New Zealand. What happened in not a few cases was that a medical man, anxious to help the statistics, notified a goitre which happened to be present in the neck of some patient consulting him for a totally different complaint. When the doctor called attention to the goitre the patient was indignant, and especially so if any hint of notification was whispered. Many other medical men ignored the notification, or only notified marked cases. Such notification naturally was unsatisfactory and was not continued.

In going through the old pathological specimens which formerly had been housed in the Anatomy Department here I found several specimens of brook trout with large, nodular, swellings on the gill plates, labelled "Carcinoma". These fish had been taken from the Opoho fish hatchery on the outskirts of Dunedin, in 1890. On histological examination it was still

possible to recognise thyroid tissue, and the appearance and position of this recalled the work of D. Marine and Lenhart on fish goitre, (1),(2),(3),(4). More recently I found a similar condition occurred in fish in the Acclimatisation Society ponds in Christchurch, (see Photograph Album, figs.154-157 ).

About this time I learnt, quite accidentally, from a member of my pathology class, that goitre, or at least something resembling it, had occurred amongst lambs near Balclutha - South of Dunedin. The story of this approximated to that of the "Foetal Athyrosis" described by Ennis Smith (5).

Thus goitre seemed to occur here in animals and fish as well as to be prevalent in human beings.

Towards the end of 1918 the observations by Marine and Kimball on the prevalence and prevention of goitre in school children in the Great Lakes district of America came to my notice, (6),(7), and I approached some of the school medical officers to see if they would make similar systematic observations of the necks of children. Unfortunately our influenza epidemic disorganised most things for a considerable period about this time and no satisfactory systematic observations were made until Dr. C.E.Hercus, now my colleague here as professor of Bacteriology and Preventive Medicine, made in 1920, (8),(9), extensive investigations on these lines in Canterbury district, and especially in Christchurch. Similar investigations have been made by Dr. Mecredy, school medical officer, for various districts in Otago (10). These results will be discussed later.

Being thus attracted to this subject by its apparent frequency it seemed necessary that an attempt should be made to answer certain basic questions.-

1. What is the nature of the goitre in New Zealand, and does it correspond morphologically with goitre elsewhere ?
2. What is the incidence of goitre and how is it distributed ?
3. Has goitre any relationship to infection, food, water, etc.?
4. What position does Iodine hold in relation to goitre ?
5. What is the distribution of Iodine, and its mode of assimilation ?

There are many other questions that arise, but, for practical purposes, a few of the more general had to be taken first, in view of work already done especially in America and Switzerland.

So far as at present possible, answers to the questions mentioned will be given in the subsequent sections of this thesis.

Certain difficulties have presented themselves and are being overcome only slowly. The literature on goitre has grown to formidable dimensions; and literature, especially continental papers and the earlier works, is very incompletely represented here at present; no attempt, therefore, will be made to give a complete bibliography. Fortunately this is not so serious an omission as at first sight appears, as many of the more recent papers refer, often at length, to previous work; also, for the particular points of interest here it is more important to record the local facts than to review exhaustively all previous work. Further, as the problem presented here apparently corresponds closely with that in certain parts of America, and as the work there is comparatively recent and accessible in our library, I have naturally quoted such work more prominently.

For reprints of a number of papers I have to thank my colleagues, especially Professor Malcolm; also the librarian of

Sydney University for his kindness in lending me a recent paper on iodine estimations.

Another difficulty, common to anyone having teaching and routine duties, has been lack of continuous time for research, and the occurrence of numerous and unavoidable interruptions.

As there are many collateral lines of research necessary in this subject investigation has now developed into team work.

The incidence, school, and preventive aspects have become the special care of my colleague, Professor Hercus, and the School Medical Service. The iodine distribution I am interested in still, personally, but here the Chemistry Department of the Otago University has come to our aid and the Health Department of the New Zealand Government, which has just now (April, 1924) agreed to a grant for a whole-time research chemist and for additional apparatus

Animal experiment has hardly been touched upon. Some years ago I sketched out a scheme for a team-work investigation of goitre, in which animal experiment was to be carried on 'pari passu' with statistical and other methods of investigation.

Feeding experiments to test the effect of varying amounts of iodine were to be performed, but it was soon apparent that no information was available as to the amount of iodine naturally present in food stuffs; further, so much has been done, and well done by Marine and others on iodine absorption by the perfused gland, compensatory hypertrophy and hyperplasia, involution etc. that it seemed superfluous, from our point of view, to repeat these.

The term "Goitre" ,without qualification, has been used in the title of this work. While the main interest, and the chief economic problem lies in the 'endemic' variety, and

while that has been chiefly considered here, the 'exophthalmic' type has been referred to in the pathological sections, rather in its relation to goitre generally than as a special study.

## II.

## S T A T I S T I C A L .

A. Mortality Returns.

I am indebted to Mr. Malcolm Fraser, Government Statistician, for the following tables, (A) and (B).

Table (A) gives the "Deaths from diseases of the thyroid, 1918-1922". ( See Appendix A.)

Table (B) gives the "Total number of cases and deaths of patients treated for diseases of the thyroid in Public Hospitals during the five years 1918-1922 inclusive". Also - included in above - "Deaths in Public Hospitals. (See Appendix B.)

Table (A) gives no idea of the prevalence or distribution of goitre, but it brings out the fact that, with the exception of exophthalmic goitre, comparatively few cases are recorded as dying actually from the thyroid disturbance. The deaths among females are much more numerous than among males, in the proportion of 5 : 1 for all cases; this corresponds with the fact that the incidence of goitre is much greater in females than males.

In Table (B), second part, the deaths in Public Hospitals remain at a fairly constant figure. The increase in the years 1920 to 1922 is more apparent than real, owing to the influenza epidemic at the end of 1918 increasing the number of total deaths and diminishing considerably the proportion due to thyroid disease.

Here again exophthalmic goitre is more in evidence as a recorded cause of death than all the other forms of goitre.

In Table (B), first part, it will be seen that the number of cases returned as goitre is considerable and remains fairly constant; though, if the cases recorded under "Other diseases of thyroid" be added, an increase will be noted. Here again the

female cases greatly exceed the male.

Both these tables refer to the whole Dominion, and, as will be seen later, there is considerable variation in different areas.

However, they serve to show that goitre is a common disease and one responsible for a number of deaths annually in the whole Dominion. They do not indicate the prevalence of the malady or the amount of incapacity produced by it.

#### B. Recruiting returns during the War.

In Appendix C are the figures referring to the rejection of recruits for goitre. These figures cover the period from the beginning of the Ballot - November 1916 - to the end of the Ballot - November 1918. The rejection was from Class A, i.e. those fit to serve overseas.

This table ( Appendix C ) is very interesting. In it the recruits are divided into the four military districts, corresponding approximately to the four old Provincial Districts.

A marked difference is seen between these, Canterbury being easily highest with 1009 rejections for goitre out of 31,739 men examined, i.e. 3.179% ; and Otago comes next with 1.437 % .

Differences also appear between the various occupations - thus, the medical profession had no rejections out of 216 examined, and police officers were equally free, though the number examined - 52 - was small. These two groups are, however, more or less of selected individuals. More striking is the relative immunity of seafaring men who show but two, or 0.08 %, rejections out of 2309 examined. This group cannot be regarded as in any way selected and yet so far as goitre is concerned they are relatively immune. Compare these with the plasterers ( 9 out

of 266, or 3.36 %), the printers (27 out of 1080, or 2.50 %), or the woolclassers and sorters (9 out of 337, or 2.67 %). I can offer no satisfactory reason why the incidence among plasterers should be so high. Printers certainly might be said not to work under ideal hygienic conditions, but why the high incidence (2.67%) among woolclassers and sorters ? Data as to nature of food, surroundings etc. are not available with regard to the various groups of men, so any attempt at etiology is at present premature.

However, the table furnishes the starting point for future investigation into industrial hygiene in relation to goitre.

When the official document (11), (See Appendix D. ), from which the above table was constructed, is consulted it will be seen that no other cause of rejection shows a similar geographical distribution. Thus, if table '5' on page four of this document be examined, it will be seen that there is no correspondence between goitre and "Defects in extremities", "Under height", "under chest measurement", "Insufficient weight", or indeed any of the causes of rejection : indeed, in all these causes specified Auckland District shows many more rejections than Canterbury or Otago and yet its rejections for goitre are only 50 (out of 23'682 examined ).

Thus, from the data here available, it appears that Canterbury District, and to a less extent Otago, may be regarded as distinctly goitrous as compared with the two Districts Wellington and Auckland.

This might suggest a difference in the prevalence in the two islands, but Wellington District is not strictly North Island as it embraces Nelson in the North of South Island.

This table shows that goitre is prevalent even amongst males of military age, and has a distribution, similar in the main to that which will be shown for school children.

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I have to thank the Director General of Medical Services (.N.Z) Sir Donald McGavin, for data, both the official files and additional details: also the Acting Chief Health Officer (1919), Dr. Makgill, and Dr. Frengley, Deputy Chief Health Officer, for further details kindly placed at my disposal.

### C. Notification of goitre.

For the details see Appendix E.

I have to thank Dr. Watt, Director of Public Hygiene in the Health Department, for these figures, and I have quoted his comments.

As already indicated, notification of goitre was not a success as far as getting an idea of its prevalence and distribution was concerned. The notification was voluntary and many cases were not notified. In some districts, owing to the enthusiasm of the local medical men, the majority of goitres were returned, in other districts notification was very perfunctory. Thus the data obtained have little real value. It is of interest, however, to notice that Canterbury again heads the list in total cases notified and in the percentage.

Realising the drawbacks of this method of getting data as to prevalence and distribution of goitre the Health Authorities withdrew the notification after a comparatively short trial.

### D. Hospital Returns.

For the details see Appendix F.

With the intention of getting some idea of the prevalence, distribution, and types of cases of goitre seeking hospital

/ treatment

treatment I scrutinised the hospital returns for recent years. I had hoped to have the four main hospitals ( Auckland, Wellington, Christchurch, Dunedin ) represented, but, as the returns from Wellington Hospital did not come to hand, they have been, perforce, omitted. I have to thank the Medical Superintendent of Auckland Hospital for permission to use his hospital case records, and my former pupil, Dr. Dudding, house surgeon in that hospital, for the trouble he took in getting out the details of individual cases for me. My thanks are also due to the Superintendent of Christchurch Hospital, and to Dr. Comrie, another pupil and former house surgeon, for details of cases of that hospital; and to Dr. De'Ath, house surgeon in Dunedin Hospital for details of cases there.

From the details so furnished I have constructed the tables shown in Appendix F.

For the sake of convenience I have taken only round figures of the total cases of all kinds admitted to these hospitals; the actual figures are slightly greater but this does not appreciably affect the result.

Here again Christchurch - which is the main centre of Canterbury Province - heads the list with 1.014 % of goitre cases, Dunedin comes next with 0.80 %, and Auckland last with 0.35 % .

It will be noticed that the total number of goitre cases admitted to Auckland Hospital in six years is less than that at Dunedin in four, or Christchurch in three years.

The proportion of exophthalmic goitres is considerable in each hospital but this rather due to the nature of the trouble than because it is the most prevalent form of goitre. In Christchurch 53.29 % of the total cases were simple (non-toxic) goitres. In classifying these cases I have adhered to the

usual clinical groups which are employed in the hospital classifications.

In all instances the female sex preponderates considerably, especially in the "Toxic" and "Simple" groups.

The average age of the three main groups is fairly uniform.

The great majority of cases are New Zealand born and, if born elsewhere, the detailed records show, in nearly every case, that the goitre had only been noticed after they had lived some time in New Zealand.

Naturally each hospital draws mainly from its own town or the surrounding country so that the figures give some idea of goitre in each district.

The time the goitre has been noticed is very variable in all cases and the figures given are only a very rough indication of the actual duration of the goitre. Personally I have seen people - not seeking advice for goitre - in whom there was a very distinct goitre of which the individual was quite ignorant, so that any statement by the patient as to duration must be accepted with reserve. On the other hand it is not infrequent to get the statement that the goitre had been present since childhood.

There are many cases of goitre treated in private hospitals and still more, of lesser degree, either not treated at all or attended at their own homes by private practitioners. Of these, naturally, the public hospital returns give no information.

E. Statistics of Goitre among School Children.

For the details - tables and graphs - see Appendices G,H,I.

The first extensive work on this aspect of goitre in New Zealand was done by Drs. C.E.Hercus and Eleanor S.Baker in Canterbury and the West Coast area of South Island (loc. cit. 9); In Appendix G are two tables and two graphs taken from their article: to table II I have added an appendix table to show the average of Primary and Secondary schools.

This investigation shows a remarkably high incidence of enlarged thyroids in school children in these areas, particularly in Canterbury and around Christchurch and the plains south of that city. There is an interesting exception at Heathcote school, which is quite close to Christchurch and which differs from it only in the fact that the water supply of Heathcote has a higher saline content owing to slight admixture with sea water.

The water supply of Christchurch is largely artesian, that of the plains south of it is largely river water. Christchurch's supply is remarkably pure both chemically and bacteriologically.

The graph brings out a very interesting difference in the sexes. To quote the article referred to - "It (graph II) shows that throughout all age periods the number of incipient goitres in males exceeds that in females, and that from the ages of six to fourteen there is a steady fall in the number of incipients for both sexes, with a corresponding rise in the larger types. In males from fourteen onwards the incipients commence to rise sharply and the other types to fall as quickly. In females the opposite effect is seen."

A similar study of goitre in school children was carried out by Dr. R.J.R.Mecredy (loc.cit. 10), then school medical officer in Otago

in Otago district and his results in tabulated form are shown in Appendix H, with the percentages of total goitre for each school filled in by myself.

These tables are also instructive, for, while the actual numbers in many schools are small the totals for districts show certain marked differences. Thus, the Upper and Middle Clutha groups are much higher than the North Otago, Waikouaiti, Dunedin and other groups.

For the remaining figures and attached information I am indebted to Dr. A.G.Paterson, Director of School Hygiene in the Health Department, Wellington. ( See Appendix I.)

Dr Irwin, now school medical officer at Dunedin, has furnished me with many additional figures for the Otago area. Dr. Hercus independently examined some of the same schools at Balclutha and his findings closely parallel those of Dr Irwin.

From these various sources I have constructed maps showing the geographical distribution of goitre in school children, but these will be referred to later along with the iodine distribution.

III. GOITRE SPECIMENS RECEIVED AT THE DEPARTMENT  
OF PATHOLOGY, OTAGO UNIVERSITY, DUNEDIN, N.Z.

See Appendix J for details and tabulated results.

In the appended analysis a number of specimens have no data. It will be seen that many are from private sources or sent from a distance, and, in such cases it was often impossible to get the facts of the case.

The "Sources of material" gives no indication of the frequency of goitre, as not all specimens removed were sent to the laboratory even in Dunedin, and only a certain number of their total were sent from outside sources.

Again the female sex greatly preponderates. The age periods that show most specimens are 21 - 40. The "Duration of goitre" is not reliable for the reasons already given when commenting on hospital statistics.

I have grouped the cases into five groups according to their clinical condition or the data available. Thus Group I, Simple (non-toxic) includes cases where there were pressure symptoms or where the goitre was merely unsightly and was removed for aesthetic reasons. Group II, Toxic, is where the cases had the usual toxic feature clinically, but no exophthalmos. Group III, are the exophthalmic goitres, varying from slight to severe. Group IV, are cases of definite malignancy, pathologically or both clinically and pathologically, irrespective of whether or not they had also pressure or toxic symptoms as well. Group V has been necessary owing to lack of clinical data and the cases are placed merely in numerical order as received.

The pathological grouping is based on the histological study of various parts of the goitre and the several headings will be / discussed in

discussed in greater detail in the next section where a similar arrangement obtains. A "+" sign indicates that the particular histological appearance is present but does not indicate the amount or extent of such change, except that, if one + sign only be shown it will mean that the whole specimen presents but one type of appearance.

By adding the + signs together a comparison is possible between the three main clinical groups, and it will be seen that the distribution is as follows.-

	Group I (Simple).	Group II (Toxic).	Group III (Exophth.)
<u>Total Number,</u>	57	58	41
Atrophy,	34, 59.12 %	30, 51.72 %	11, 26.82%
Colloid,	50, 87.71	49, 84.48	22, 53.65
Hyperplastic Colloid,	25, 43.85	21, 36.20	22, 53.65
Hyperplasia,	5, 8.77	21, 36.20	27, 65.85
"Adenoma",	9, 15.78	26, 48.82	2, 4.87
Degeneration,	14, 24.56	18, 31.03	6, 14.63
Fibrosis,	38, 66.66	40, 68.96	15, 36.58
Haemorrhage,	30, 52.63	29, 50.00	13, 31.70

From these figures it appears that hyperplasia increases progressively from the simple to the exophthalmic groups. Group II, (Toxic) has a much higher proportion of "adenomatous" change than Groups I or III. Groups I and II are fairly equal as regards colloid appearances, fibrosis, degenerative changes, and haemorrhages, Group III having less of all these features. Hyperplastic colloid does not vary very greatly in any group, though the exophthalmic cases show the highest figure.

One or two cases of this series are somewhat unusual and worth calling attention to.- In Group I (Serial No.144) is an example of a thyroid enlargement due to hydatid cyst. This was a specimen sent in from the country with no details and the thyroid is merely an atrophied colloid gland with fibrosis around / the hydatid

the hydatid cyst. This cyst was the size of a hen's egg and contained numerous scolices.

X  
In Group V (Serial No. 171) occurs a specimen showing only chronic inflammatory changes due apparently to tuberculosis, there being definite tuberculous follicles in the fibrosed areas. This was from an outside private case and I was informed by the medical attendant that the gland was very hard clinically and was removed as being possibly malignant.

/ Section IV.

#### IV. MACROSCOPICAL AND HISTOLOGICAL CHANGES IN GOITRES.

Note.- The figures given in this section refer to the figures in the album of photographs accompanying this thesis.

In the preceding section the general grouping of goitre specimens received at the Pathology Department has been mentioned, viz. three main divisions according to the clinical picture.

No attempt has been made, or will be made, to establish separate pathological groupings. Instead the pathological changes will be discussed and, later, their relation to iodine content of the specimens.

It was outside the scope of this work to investigate the finer changes in the thyroid cells, such as the significance of mitochondria, on which Goetsch (12) laid stress in toxic thyroid adenomata; or the position, or mode of occurrence of secretion vacuoles or granules as described by Takagi (13) in dogs, Ferguson (14) in fishes, and Bensely in opossums (15) and (16).

It is also redundant to detail the normal anatomy, and histology of the thyroid when such is so ably set out by Sir E. Sharpey-Schäfer (17), Swale Vincent (18), Biedl (19), and others. The recent description of the structure of the unit of the thyroid by G.Scott Williamson and I.H.Pearse (20) is instructive and presents the unit of the thyroid in a way which may be of help in the elucidation of some factors involved in goitres.

Various classifications of thyroid changes have been put forward from time to time, but they are all catalogues of the changes that may be found in the thyroid rather than classifications.

In spite of the more recent excellent work done and correlation shown between pathological changes and clinical or functional disturbances by Louis B.Wilson (21), L.B.Wilson and Kendall (22),  
/2W.M.Boothby

W.M.Boothby (23), E.Goetsch (24), H.S.Plummer (25), and the earlier work by W.S.Greenfield (26) in the correlation of the histological changes and clinical features of exophthalmic goitre, and Kocher (27), on the histological and chemical changes in exophthalmic goitre, the statement by Marine and Lenhart (28) is still appropriate. In the introduction to their paper they say.-

"Our conception of a satisfactory anatomical classification of thyroid changes is a scheme, composed of the major types of changes observed, arranged in the order of their manifestation and in which all separate or individual observations may find proper grouping. It is universally admitted that such a classification does not exist. It is, however, in connection with that group of anatomical changes embraced under the general term "goitre" that the greatest confusion exists.

"Studies based on large series of thyroids from the lower animals are still too few, though fortunately they are increasing because observers are realising that human material is too complicated, and that the cataloguing of the almost infinite variety of possible histological variations has not simplified existing classifications or established the sequential relations of these changes. The multiplicity of terms now in use for each type of thyroid change is merely the result of this cataloguing process to which Virchow (Die krankhaften Geschwülste, 1863, iii, 4)

a half century ago called attention in the following words: 'With reference to true goitre the opinion has long been held that it comprises a series of definite changes (struma lymphatica, cystica, ossea, vasculosa, etc.) which can develop independently of each other. This is wrong. All these so-called varieties are only different modes of development of essentially the same form of goitre. They (the so-called varieties) mean only different forms of terminal conditions or metamorphoses which can be combined with one another in the same tumour, and a very large and striking variety of these metamorphoses may exist in the same tumour (goiter)'

"While numerous and complicated anatomical classifications of human goitre have appeared since Virchow thus wrote, and while the literature has been enriched by many detailed descriptions of histological changes, it does not appear that the really fundamental types of change and their sequential relations are yet established.

"Several have been and still are operating to retard our fuller appreciation of these fundamental or major anatomical groups. Among these factors may be mentioned the following: 1. We are still ignorant of the essential cause of goiter. 2. Human, surgical material is so complicated and pure types of thyroid changes are so rarely observed in man that it has been impossible to reconstruct the primary changes from these terminal conditions. The recognition and appreciation of the primary or fundamentally important changes can be brought about only by the extensive study of autopsy thyroid series or series from the lower animals. 3. In order to interpret the anatomical changes it is necessary to correlate them with the functional activity of the thyroid, and definite criteria of such functional activity are by no means easy to determine. The best that can be done at present is to compare the iodine contents with their corresponding histological structures in large series of glands. 4. In the correlation of the clinical manifestations of goitre with the anatomical findings the probability has not been borne in mind that the thyroid changes are the result of a systemic disturbance instead of the cause of the systemic disturbance. 5. It does not seem possible at the present time to distinguish or to separate, solely by anatomical studies, those thyroid hyperplasias which should be considered as tumours from those which should be designated as physiological or compensatory hyperplasias. This fact is implied in the use of such terms as "adenomatous" or

"adeno-parenchymatous" goiters. 6. The thyroid undergoes exceedingly rapid histological changes the causes for which are still ill understood. Thus an active hyperplasia with high columnar epithelium and no stainable colloid may change to a colloid gland with low cubical epithelium and abundant colloid in from two to three weeks.

"All these factors introduce grave difficulties in the way of establishing the major and fundamental types of thyroid changes. Nevertheless, by the utilisation of material from human autopsies and from the lower animals, together with our present accumulation of experimental data, it is possible to overcome the major difficulties and to separate the essential and major types of anatomical changes from the minor and secondary changes which thyroids in common with other tissues may undergo. "

They then give a classification as follows:-

- I. Normal Thyroid.
- II. Active Hypertrophies and Hyperplasias (goiter).
  - 1. Developing from the normal thyroid.
  - 2. Developing from the colloid gland (goiter).
- III. Colloid Glands (Goiters).
- IV. Regeneration (Hyperplasias).
- V. Atrophies:
  - 1. Premature atrophies
    - (a) of obesity
    - (b) of cretinism
    - (c) of myxedema
  - 2. Senile
- VI. Degenerations:
  - 1. Hyaline
  - 2. Amyloid
  - 3. Calcareous, etc.
- VII. Inflammations:
  - 1. Acute thyroiditis
  - 2. Chronic thyroiditis
- VIII. Tumours:
  - 1. Benign
    - (a) Fetal adenoma
    - (b) Simple adenoma
  - 2. Malignant
    - (a) Carcinoma from fetal adenoma (carcinoma simplex)
    - (b) Glandular carcinoma
    - (c) Sarcoma

/ (d) Endothelioma



Wilson and Kendall (loc. cit. 22) give the following clinical classification.- " (1) Hyperplastic toxic ("exophthalmic goitre"); (2) Non-hyperplastic toxic, with high blood pressure; (3) Non-hyperplastic toxic, with low blood pressure ; (4) Non-hyperplastic, questionably toxic, with low blood pressure; and (5) Non-hyperplastic atoxic, with low blood pressure," following the arrangement of Plummer (loc. cit. 32) and a simplified classification on the basis given by Wilson as quoted above.

While Allen Graham (31) gives this classification, adapted from Marine, (loc. cit.)-.

- " 1. Normal.
- 2. Hypertrophy.
- 3. Hyperplasia.
- 4. Colloid goiter.
- 5. Exhaustion, atrophy, fibrosis.
- 6. Adenoma, benign
  - Type A. Diffuse colloid adenomatous goiter.
  - Pure fetal.
  - Type B. Fetal, Intermediate.
  - Colloid.
- 7. Adenoma, malignant.
- 8. Carcinoma.
- 9. Sarcoma.
- 10. Inflammation. "

In the routine goitre specimens examined by me and in the cases where the iodine content of the thyroid was estimated I have made the arrangement in groups according to the clinical condition. As blood pressure examinations were not made as a routine I have not been able to attempt any division of toxic and non-toxic cases according to their blood pressures. The chief fundamental changes are indicated in columns opposite the individual cases of the groups.

The frequency of the different pathological changes in the groups has already been mentioned, but some more detailed explanation of these changes is now necessary.

Colloid.- is the condition of acini (or alveoli, or follicles- I have used the term "acini" throughout ) where the epithelium is flat or low cubical and the content of the well known colloid character, varying from faintly-staining or thin, to deeply-staining or dense. According to de Quervain (33) the capacity of the colloid for taking stain is, in a general way, in a reversed relation to its physiological activeness.

Various changes may occur in the colloid - vacuolation, fragmentation, splitting, and irregular staining. Splitting is usually an artefact due to the density of the colloid and difficulty in sectioning it, ( Figs. 57, 62, 66, 84, 109, 115, 129, etc. ). Vacuolation and fragmentation are degenerative or atrophic changes, ( Figs. 76, 80, 88, 94 etc. ). Irregular staining may be due to differences in density or to haemorrhages. S.Wail (34) has already drawn attention to these alterations in the colloid and concludes that the appearances are physical rather than chemical.

The term "Colloid" is used without reference to whether it is a normal, an atrophied or an enlarged acinus which contains the colloid.

A good example of a "Colloid Goitre" (clinically- "Simple, non-toxic") is given in D.B.1/827, ( Figs. 126, 127, 128 )

Note on Size of acini.- In the detailed descriptions of the histology of the Iodine Content Series (Appendices M and N ) the adjectives 'small', 'medium', and 'large' are used. In order to have some quantitative basis for these terms acini were measured and the following measurements obtain.-

Small = up to 0.05 mm. or 50 $\mu$

Medium = 0.05 mm. (50 $\mu$ ) to 0.2 mm. (200 $\mu$ )

Large = over 0.2 mm. (200 $\mu$ ).

/ If these sizes .

If these sizes be compared with the average normals limits as given by Sharpey-Schäfer (35) 0.045 to 1.0 mm. , or Swale Vincent (loc. cit. 18) 45 $\mu$  to 110 $\mu$  (v. Ebner & Kölliker) or 80 $\mu$  to 220 $\mu$  (Simon) - i.e. 0.045 mm. to 0.22 mm., it will be seen that the "Medium" acini fall within accepted normal limits, while the "Small" acini are below, and the "Large" above these limits.

Hyperplasia.- has its usual meaning in pathological processes, viz. an increase in number of elements. I have hardly used the term "Hypertrophy", though the qualification "large" as defined above implies an increase in size or hypertrophy of the acinus. It is very difficult to separate hypertrophic and hyperplastic processes and, as an increase in size of an acinus so frequently implies either a present or previous increase in number of its cells, its hypertrophy as a whole has been due to hyperplasia of of its elements. The term is used also where the acini are often small but numerous and the individual cells high cubical or columnar, usually with thin or no colloid, e.g. in the typical picture given by exophthalmic goitre ( See figs. 39, 40, 123.).

Hyperplastic Colloid.- indicates a colloid acinus in which the epithelium is as seen in the hyperplastic acinus, viz. high cubical or columnar, sometimes with papillary processes projecting into the lumen. It may be taken as an indication of activity in the epithelium of the colloid acinus. Frequently colloid acini with flat epithelium at one side and columnar epithelium opposite. Numerous examples of this occur in the specimens examined, e.g. D.B.1/2619 (Fig.8), and D.B.1/1856 (Figs. 13 and 14), also Figs. 28, 65, etc. This is the appearance described and figured by Marine and Lenhart (36) as "Colloid-glandular hyperplasia" and they subdivide it into 'early', 'moderate', and 'marked'.

/ It may

It may indicate either the reversion of a resting colloid acinus to activity, or the involution of an hyperplastic acinus to colloid. It is not possible from the histological appearances alone to say which way the process is going.

Adenoma.- While this term is used to indicate similar histological formations to those described under this term by Marine (loc. cit.) and others it is not to be understood that one agrees entirely with their assumption that such formations are true tumour growths. It is a convenient term to indicate a localised area of growth, either past or present. The "adenoma" may be composed of small acini, closely packed together, of cubical cells with clear lumen showing no colloid - the so-called "Foetal Adenoma" (Billroth, 37.)-from the resemblance of the cells and acini to those seen in the foetal thyroid. These are assumed to arise from undeveloped acini between the regular adult acini - the intervescicular tissue or Wölfler's rests. Swale Vincent (loc. cit. 18) in the first edition of his work called attention to the resemblance of this tissue to parathyroid. Sharpey-Schäfer in 1924 (loc. cit. 17) says with regard to this intervescicular tissue that "this is partly areolar tissue with some lymphocytes, also some cells resembling epithelium of vesicles, although their identity has not been established. They have sometimes been supposed to be of a parathyroid nature, but this is certainly not the case. " The conception of Williamson and Pearse (loc. cit. 20) with regard to this "intervescicular" tissue is more satisfying. By serial sections and special fixing and staining methods they demonstrate continuity between the solid, non-vescicular or undifferentiated epithelial masses and the distended, vesicular / areas.

areas. They regard the former as parts of the epithelial cords or columns of the thyroid unit which have not yet become distended by secretion or colloid. This conception is further supported by the thyroid transplantation experiments of Hesselberg and Loeb (37,a.); also it helps to explain the "Diffuse Adenomatosis" described by E.Goetsch (loc. cit. 24) where tissue resembling "adenomatous" tissue occurs diffusely amongst the ordinary thyroid acini, and where, clinically, the effect is similar to that which may occur with the ordinary type of adenoma.

( See figs. 2, 3, 6, 10, 11, 25, etc. and figs. 133 and 136 for the gross appearances of "Adenomatous Goitre".)

The other type of adenoma, described by Marine and Lenhart (loc. cit.) as "Simple Adenoma", is that with colloid acini resembling the normal colloid acini of ordinary thyroid, (Fig. 78).

Intermediate forms may occur between the "Simple" (or "adult") and "Foetal" types, and all sorts of admixtures are found.

Both types of adenoma have a "capsule", varying considerably in amount in different cases. This capsule consists of condensed fibrous tissue, in which are very frequently found atrophied remnants of acini. Many examples of this are illustrated - see above mentioned figures.

Cysts have not been separated out in the analysis though the term is frequently used to describe gross appearances, or histologically much distended acini. Some adenomata appear as cysts, also degenerated areas may become cystic; but it did not seem necessary to accentuate this appearance by giving it a separate column as the essential changes dealt with in the columns given embrace cystic appearances.

Degenerations.- These are very common in the "adenomata" but may occur apart from them. They need hardly be described in detail as they conform to the usual pathological changes of this type elsewhere. Mucoid softening of the supporting tissue is common (Figs. 31, 101 ). Calcification occurs in the older parts, particularly in the stroma and capsule of old-standing adenomata (Figs. 23, 29, 30 ). Hyaline change is also seen in the older fibrous parts (Fig. 29 etc.). Fatty change is common, both within the acini and in the supporting tissue. It may be in the form of ordinary neutral fat or doubly refractile lipoid; sometimes acini are found filled with fat or lipoid-laden cells ( Figs. 13, 16, 17. ).

Fibrosis.- This is frequently a precursor of the degenerative changes and an accompaniment of atrophy, but it has been mentioned separately as it seems worthy of more consideration than often accorded it. It is seen around "adenomata", though it is here frequently - and probably always in the first instance - a condensation of pre-existing stroma rather than an increase, the atrophy of acini leading to a collapse of structure and consequent apparent increase of fibrous tissue (Figs. 2, 11, 22, 76 etc. ).

An analogous condition is seen in the arteriosclerotic kidney.

A frequent precursor of fibrosis is haemorrhage, which, after organisation leads to fibrosis. This is probably the explanation of most of the dense scars seen ( Figs. 18, 35, 71, 72, 93. )

Haemorrhage.- The frequent occurrence of this in goitres is remarkable, but is easily appreciated from the structure of the / gland.

gland. As shown by all who have described the anatomy and histology of the thyroid it is very vascular and the capillaries lie close up against the epithelium of the acini, both in normal and in abnormal thyroids (Figs. 14, 25, 26, 50, 51, 55, 56.).

In specimens received from operation haemorrhage undoubtedly occurs from the operative manipulations, but, excluding these, spontaneous haemorrhages are very frequent. They are met with in post mortem specimens (e.g. Fig. 64) as well as in operation specimens of goitre. They may be seen easily in the naked-eye specimen (Fig. 136), or found only microscopically.

Haemorrhages may occur either into the stroma or acini, particularly into enlarged acini (Figs. 1, 12, 13, 19, 32, 36, 43.)

Remains of previous haemorrhage are seen either as condensed organising clot (Figs. 12, 31.), or as pigment granules, these usually lying in the fibrous tissue which may be young or old depending on the date of the haemorrhage (Figs. 23, 72, 93, 94.)

Atrophy.- This is a term which, as Marine and Lenhart explain (loc. cit.), should not be used for a merely resting gland or one which has involuted from a previous active state. It is applied to glands, or portions of glands, which have regressed to a state where, presumably, they are of little use.

Complete atrophy as in advanced cretinism does not appear in this study but atrophy of groups of acini, or individual acini, is very frequent.

Atrophy may occur in small, previously hyperplastic, acini (Fig. 29) in which case the cells become attenuated, flattened, and finally disappear; or in colloid acini, when the epithelium becomes thread like and the colloid either dense dense (Figs. 90, 94), or granular ( Fig. 101), or fragmented (Fig. 32). Enlarged acini may become /atrophied

atrophied (Fig. 148).

In the "capsules" of adenomata are frequently seen atrophied remains of acini, either as a few attenuated cells, or as small colloid spaces (Figs. 2, 9.)

Other changes that are frequently seen but which have not been specially tabulated are.-

Congestion.- This is a common feature especially in hyperplastic and hyperplastic colloid areas (Figs. 13, 14, 25, 26.), but may occur apart from any special thyroid change, as seen in a number of post mortem specimens (Figs. 50, 51, 55, 61.)

Lymphoid Collections.- These have been mentioned by many workers as a feature of exophthalmic goitre thyroids, but they may occur in any goitre, particularly in atrophied or degenerating areas ( Figs. 1, 102.).

Shedding of epithelium.- is seen as a toxic or autolytic effect especially in post mortem thyroids, but may occur in goitres, particularly in the hyperplastic and hyperplastic colloid areas. L.B.Wilason (38) mentions that he has noticed a direct relationship between this shedding off of epithelium into the alveolar space in hyperplastic goitres and toxic effects clinically. I have not been able to find any such relationship in the cases studied.

Malignancy- The cases showing this pathological change have been grouped separately (Group IV in Appendix J.)

They amount to 2.2 % of all the goitre specimens. Considering the active cellular changes that are occurring in so many goitres it is rather surprising that they do not show malignancy more frequently.

Without comparing the actual figures, my impression is that

/ abnormal involution

abnormal involution (chronic interstitial mastitis etc.) of the female breast is a much more common precursor of cancer in that situation than is goitre of cancer in the thyroid:

Crotti (39) quoting various workers' figures states that "In 90 % of cases malignant goitre develops in an already pre-existing goiter, consequently it is more frequently found in regions where goiter is endemic," further, "Malignant degeneration degeneration of goiter occurs mostly between the ages of forty and sixty years", though Hughes (40) reports a papilliferous carcinoma, with secondary deposits in lymph glands, in a girl of thirteen years.

The commonest form of malignant tumour is carcinoma which is said to form 95 % of all malignant tumours of thyroid (Graham, loc. cit. 31 ). No case of primary sarcoma of thyroid appears in my cases, but four cases of carcinoma occurred, one of which is illustrated (No.180, D.B.2/1189, Figs.137 to 142 ).

Langhans gives a detailed and excellent description of thyroid carcinoma in his article "Über die epithelialen Formen der malignen Struma" (41) and figures the epithelial columns with capillary network between them, appearances well seen in one of my cases (Figs. 138, 139.).

In 1908 A.C.Hudson (42) described several cases of thyroid carcinoma, one being of squamous cell type and one having the appearance of normal thyroid but with metastases. His cases, 9,10,11, and 12 - as far as the illustrations show - look more like ordinary hyperplastic "foetal adenomata" than carcinoma, though one quite realises how difficult it often is to decide, from one part alone, as to whether an "adenomatous" area is malignant or not. Hudson refers to the oft quoted case of von Eiselberg's (43) where secondary deposits in the sternun relieved

the cachexia strumipriva following total excision of thyroid for carcinoma; the secondary deposits were composed of columnar cells with colloid and proved functionally active.

L.B. Wilson (44) also draws attention to the resemblance between benign and malignant adenomas, both in origin and appearance. He describes three stages, (i) irregularly arranged epithelial cells separated by thin-walled blood vessels, (ii) cordon-like masses, and (iii) formation of acini and colloid. In another paper Wilson (45) reviews the literature and gives numerous illustrations of the types of malignant tumour found in the thyroid. He has collected 971 cases but thinks many more have probably not been reported. In the Mayo Clinic, of 290 cases, 158 had goitre before age 30, and 106 in the next two decades: 159 had had goitre for age ~~five years or more~~, while only 64 patients had not noticed enlargement previous to the diagnosis of malignancy.

Unfortunately in my four cases I have few clinical details; in one case - sent from the North Island - none at all; but three, at least, are females over fifty, and two were known to have old standing goitres. All, except the last, turned up accidentally in the routine examination of specimens sent to the laboratory.

In the last, which is the subject of the illustrations, I was informed later by the surgeon who removed it that the growth was fixed to, and evidently infiltrating the trachea, and great difficulty was experienced in removing it. The patient recovered from the immediate effects of the operation but died shortly afterwards. There was no post mortem possible.

Fig. 142 gives an idea of the gross appearances of the specimen, the solid parts (A and B) were pale, firm, and showed the large surface veins plugged with tumour. The other lobe (C)

/ looked like

looked like an ordinary "adenomatous goitre", but in some of the nodules were white areas which proved to be early carcinomatous growth. The microscopical appearances of the various parts are shown in Figs. 137 to 141, including a portion of the plugged vein (Fig. 139). Although many parts of the tumour show simply small epithelial cells with relatively large, deeply staining nuclei - just as described by Wilson (loc. cit. 44) - some have a more definite arrangement and appearance of secretion or colloid between them ("a", fig. 138).

In all the foregoing histological work the usual technique for report material in my laboratory was employed. Several pieces were taken from different areas of the specimens and cut in various planes. Formalin, either 5% in saline, or in the form of Pick's solution was used as fixative. In a few cases corrosive, or picro-corrosive was employed. Embedding was in paraffin after the usual alcohol and xylol stages. Frozen sections also were made of many specimens where fat was to be demonstrated especially. Staining was by the routine Haematein and Eosin, and Iron-Haematoxylin (Weigert) and Picro-fuchsin. In some cases Giemsa was employed, or bacterial stains where such were indicated.

The object was to get a general view of the changes rather than to make a detailed cytological study; also to compare types of change found with the iodine content; and finally to see whether the changes found in goitres in New Zealand corresponded with those described elsewhere.

Further discussion of the histological changes will be reserved till the Iodine Content has been considered in the following section.

## V. IODINE CONTENT OF THYROIDS.

See Appendix K for tabulated results of Iodine Content and histological changes.

In Appendices M and N will be found the details of all the specimens of thyroids examined as to their Iodine Content and histological changes. The Album of Photographs contains illustrations of these changes.

Baumann (46), nearly thirty years ago found, in Freiburg that the thyroids of twenty six adults contained iodine in amounts varying from 0.22 to 7.2 mgm., average 2.5 mgm., while the thyroids of four others contained 10.8, 14.9, 19.9, 35.3,mgm.

Of thirty four adults in Hamburg the thyroids of thirty contained 0.3 to 9.7 mgm. per gland, average 3.83 mgm. The four others contained iodine in excess of 10 mgm., the largest being 27.6 mgm. In Berlin, eleven adults showed less than 10 mgm., average 6.6 mgm., and two others showed 14.1 and 22.7 mgm.

He showed that iodine was a normal constituent of the thyroid and that it occurred in the colloid.

Baumann also found that thyroids of children usually contained little or no iodine and that the presence or absence of iodine and the amount when present varied according to the locality from which the glands were obtained.

H.Gideon Wells (47) noticed, in the thyroids of six children under four years of age, from Chicago, that three contained only traces and three had from 0.011% to 0.092% of iodine.

Oswald (48), employing Baumann's method, studied the relation of iodine content to goitre, and (49) by a separation of / the proteins

the proteins of the thyroid on a basis of solubility he isolated a product he called Thyreoglobulin having, in his opinion, the physiological action of the dessicated thyroid.

Kendall (50,51,52,53,54.) in a series of papers describes his researches on the isolation of the thyroid hormone which he finally obtained in pure crystalline form and called Thyroxin .

He describes it as a comparatively simple substance, three iodine atoms being firmly fixed to the benzene ring while the imino and carboxyl groups on the indol ring are mobile and vary according to whether the substance is in acid or alkaline solution.

Further, substitution of this part of the molecule by an acetyl or ureid group renders the substance physiologically inert.

In the preparation of thyroxin only about 50% of the total iodine of the gland was accounted for, the remainder possibly being in intermediate stages and certainly inert as regards physiological thyroid hormone action.

Kendall states that "The function of the iodine in thyroxin is to increase the reactivity and sensitiveness of the functioning groups present, viz. carboxyl and imino, and any other function of the iodine is highly problematical." "If the iodine per se is the essential portion of the thyroid hormone, merely replacing the H of the imino group by a derative would probably not alter the effect of the iodine in the hormone . . . . ."

Further, Kendall (loc. cit.) and others have shown that thyroxin in milligram amounts is capable of acting in the same way as dessicated thyroid gland, producing increased metabolism, pulse rate etc. and giving the picture always ascribed to excess of thyroid secretion.

Plummer (55) , as the result of his work with thyroxin in goitre cases gives an almost mathematical relationship between thyroxin and basal metabolism rate, thus one of his statements is that "The average daily exhaustion of thyroxin in the tissues is between 0.5 and 1.0 mgm." and "A shift of 1 mg. of thyroxin in the tissue of the body is accompanied by a corresponding rise or fall of between two and three per cent. in the basal metabolism." Further, "Two milligrams of thyroxin a day may hold the basal metabolism from twenty to thirty per cent. above normal;" ~~three~~ ~~milligrams~~ ~~may~~ hold the basal metabolism fifty per cent. above normal." And, "Without knowing the exact mechanism of the normal stimulation of the thyroid we can assume that it is brought into play by a drop in the amount of thyroxin in the tissues of the body. This being true, the daily administration of one milligram or more of thyroxin should place the thyroid at partial or complete rest, at least so far as the production of this agent is concerned. Following this hypothesis, the daily administration of 0.5 to 1 mgm. of thyroxin to a normal person might not be attended by any physiological reaction. We have given a daily dose of one milligram to a number of persons, apparently having a normal thyroid function, for months without any deflection of the basal metabolism from the normal."

Kendall (loc. cit. 50 etc.) noted that different samples of thyroid varied greatly in thyroxin content, e.g. analysis of samples of thyroids of animals in January, February, and March showed an iodine content so low as to make isolation of thyroxin impracticable. During the summer months the thyroxin content of the glands increased from four hundred to five hundred per cent. Thus, he found that the activity of thyroids, as judged by amount

/ of thyroxin

of thyroxin obtainable from them, was directly proportional to their iodine content.

Rogoff and Marine (56) showed the same relationship.

In colloid ox and sheep thyroids, rich in iodine, they obtained active hormone - as tested by the rate of metamorphosis of tadpoles - while from hyperplastic, lamb, thyroids containing no iodine, no activity was found although the same method of extraction of Kendall's "A" product was employed.

Lenhart (57) had previously shown the same thing with dried thyroid, that glands rich in iodine caused more rapid metamorphosis of tadpoles than glands poor in iodine content.

Attempts by Rogoff and Marine (58) to produce a thyroid-like hormone by artificially iodising proteins were only partly successful, thus iodised blood protein ("Iodalbin") produced an acceleration of metamorphosis of 21.5%.

Swingle (59) using iodine alone, or in the form of potassium iodide, or iodoform, produced tadpole metamorphosis as readily as with thyroid.

Uhlenhuth (60) in a long paper with full discussion found no such effect in development of salamander larvae, in which thyroid hormone # with its combined iodine - was necessary for metamorphosis. The difference he explains is due to the earlier development of the thyroid in tadpoles which can thus utilise iodine to make hormone.

Marine and Feiss (61), and Marine and Rogoff (62,63) found by perfusion experiments in dogs, both into the circulation in vivo and by means of the isolated thyroid that the gland very rapidly takes up iodine but it is twenty hours before any marked pharmacological activity is evinced. The amount of iodine quickly taken up and stored - and more slowly elaborated - depends on the

/ histological state

histological state of the gland. Thus, colloid glands took only eighteen per cent., while markedly hyperplastic glands absorbed no less than seven hundred and forty three per cent. The amount taken up is in inverse proportion to the amount of colloid present. The hyperplastic glands after absorption of iodine reverted to a resting colloid state. On the other hand Loeb (64,65), after excising the greater part of the gland in guinea pigs, found that the usual compensatory hypertrophy (with hyperplasia) in the remaining portions was increased by the administration of iodides but inhibited by thyroid feeding. Thymus, "Tethelin", and a meat diet did not produce any effect as compared with controls. There were considerable variations in different animals and the amount of gland removed was very large, also the results varied with the time of year when the animals were operated upon.

The various works above cited all indicate the presence of iodine in the thyroid and forming an essential part of its hormone. In all higher animals - mammals, birds, fishes - the thyroid has become the organ specially concerned with the absorption of iodine, the amount present in the rest of the body being negligible. As the animal scale is descended iodine is more diffused, e.g. in certain Coelenterata (*Obelia longissima*) iodine to the amount of 0.013% (of dried tissue) was found with no special distribution, while some annelid worms contained from 0.008% to 0.039% and the worm tubes contained much larger amounts.

In plants, also, so far as at present examined, iodine, when present, shows only a general distribution throughout the plant tissues. Sea plants show a much higher content of iodine than land forms, as much as 0.2% being found in certain *Laminaria*.

( See Cannon, 66.)

In samples of common sea weed, a large species of laminaria, from the beach near Dunedin we found 0.10 mgm. per gm. of dry material, using Hunter's method for estimating the iodine.

Sufficient has been said for the moment to show that iodine is an important and special feature of the thyroid and its hormone, and, a priori, one might expect that disturbances of the thyroid would be associated with changes in its iodine content, and, conversely, that disturbances of the iodine content of the thyroid might result in disturbances of its function and structure

With the object of comparing structural changes in the thyroid and its iodine content, and so being able to compare the New Zealand findings with those obtaining elsewhere, a number of thyroids of clinical goitre cases and of post mortem cases, not necessarily goitre, were examined.

I am indebted to my former assistant, Dr. C.S.Hicks, now Beit Memorial Scholar at Cambridge, for much of the technical part of the work; also to my present assistants, Dr. P.P.Lynch and Miss Woods, M.Sc., for their help with the routine carrying out of the various examinations.

Hunter's method was employed (67) and checked by numerous controls before the series here presented was finally worked out.

The lesser amount mentioned by Hunter, viz. fifteen grams, of fusion mixture was used. At the commencement of this work the results were not satisfactory, the end point at the titration stage being frequently indefinite. By a process of elimination the hypochlorite was found to be at fault owing to the presence of traces of manganese. When pure hypochlorite was made by passing chlorine through pure caustic soda - as recommended by Hunter when the ordinary hypochlorite is at fault - the difficulty disappeared.

Blank controls and controls with known amounts of iodine gave remarkably constant results, just as Hunter figures in his paper.

With regard to material, it was frequently impossible to get this fresh and a number of analyses were made of formalin-fixed specimens. These were afterwards discarded as it was found that some iodine escaped into the fixing solution, a fact noted by Wilson and Kendall (loc. cit. 22). All the results given, therefore, refer only to fresh material.

The surgical, or post mortem specimen, as the case might be, was received at the laboratory as soon after removal as possible and all adhering fat and capsule tissue were removed. The total fresh weight was taken and then portions were removed from different areas for histological examination, the specimen was again weighed, put into a clean evaporating dish and dried to constant weight. It was then broken up in a mortar and afterwards reduced to a fine powder in a small hand mill. One gram of this was used for each examination and duplicate examinations were done whenever the amount of material permitted. The dried sample was then treated exactly according to Hunter's method.

The results are calculated in milligrams per gram of dried material.

It was found that the weight of the dried material was approximately 23.2 % of the total fresh weight. Thus in fifteen specimens the figures were:-

<u>Fresh (wet) weight.</u>	<u>Dry weight.</u>
47.00 gm.	12.44 gm.
56.00	13.25
30.03	7.54
29.00	5.50
46.34	12.60
37.25	8.50
136.00	36.00
20.34	5.40

(Fresh (wet) weight.)	(Dry weight)	
202.00	46.30	
81.50	16.70	
11.20	2.30	
119.50	23.00	
18.80	4.95	
16.70	3.50	
<u>21.20</u>	<u>5.00</u>	
<u>872.86</u>	<u>202.98</u>	= <u>23.2 %</u>

In the tables given I have shown the weight per gram also the approximate total amount of iodine present in the specimen as calculated from the above percentage. While this does not give absolutely accurate total amounts it gives sufficiently accurate results for comparative purposes.

In this series, besides the clinically goitre cases, arranged according to the clinical types - Simple, Toxic, Exophthalmic - are a number of post mortem specimens of thyroid, several of which show pathological changes of goitre, though there was no functional disturbance noted clinically, and one ( 63, D.B.1/2993) was a fatal case of acute exophthalmic goitre. I have arranged the post mortem specimens in order of age of the patients and irrespective of the disease from which they suffered or the condition of the thyroids.

Before commenting on the figures of this series some idea of accepted standards for normal thyroids is necessary.

Sharpey-Schäfer (loc. cit. 12) quotes Symington (68) who puts the normal weight at 30 to 40 grams.

Kojima (69), weighing glands obtained from autopsy, found the average weight in non-insane persons to be from 22 to 25 grams, while in a series of insane persons the average weight was less - 16.5 grams in males and 16.87 grams in females.

Horisawa (70) studying the size and weight in 930 individuals

/ gives as

gives as average weights 17.47 grams for males between twenty six and forty two years, and 15.30 grams for females between twenty and thirty three.

McCarrison (71) states that, in the adult, "its average weight is 36 - 50 grammes in inland tracts and hilly districts, 20 to 30 grammes at the sea coast. It is roughly one-third heavier in females than in males."

With regard to normal limits of iodine content of thyroid considerable variation occurs, depending on many factors such as age, locality, food, etc. Unfortunately in the literature the percentage of iodine or the amount per gram is stated frequently without giving the total amount of iodine in the gland, though, speaking generally, a high percentage of iodine is associated with a small size of gland, usually of colloid type.

McCarrison (loc. cit.) gives 0.01 per cent as the minimum amount of iodine necessary for health and quotes Cameron as recording the maximum quantity of 1.16 per cent. and as stating that it is present in 0.3 to 0.9 per cent. of the dried gland. and 2 to 9 milligrams as the amount present in the entire adult gland.

Marine and Lenhart (72) in their study of the relation of iodine to structure in the case of adult human thyroids consider thyroids weighing 20 -30 grams "normal", between 30 and 50 grams "slightly enlarged", between 50 and 100 grams "moderately enlarged", and over 100 grams "markedly enlarged". In their normal gland the iodine content per gram of dried gland was from 3.691 mgm. to 1.307 mgm. They have shown (loc. cit. 29) a similar variation in normal sheep, ox, pig, and dog thyroids. Some of their figures for other states of human thyroids are as follows:-

/Histological type.-

Histological type.	Iodine per		42.
	Iodine per gm. dry gland,		
	Highest.	Lowest.	
	mgm.	mgm.	
Normal-early glandular hyperplasia	0.984	0.615	
Early glandular hyperplasia	1.077	0.738	
Marked glandular hyperplasia	0.584	0.118	
Colloid glands (goitres)	3.914	0.784	
Colloid-moderate glandular hyperplasia	0.492	0.184	
Normal colloid glands	3.230	1.100	

Their figures also show that the iodine content per gram weight is in inverse proportion to the epithelial activity as estimated by the degree of hyperplasia.

A similar fact is brought out in the paper by Wilson and Kendall (loc. cit. 22) where they give numerous tables of the clinical, pathological and chemical relationships of goitres, the figures - given in table VI of their paper - show iodine values between 0.02 and 0.19 per cent. depending on the presence or absence of epithelial regression and colloid formation. The total amounts of iodine in the specimens removed varied from 18.4 to 32.9 mgm. in "non-hyperplastic toxic" cases, and from 12.3 to 22.5 mgm. in "non-hyperplastic atoxic" cases.

Pellegrini (74) found iodine in three out of thirteen foetuses or newly born children; among children aged eleven days to two years fifteen out of twenty three had iodine. The presence of iodine appeared to be independent of the state of nutrition. In the thyroids of one hundred and one adults the average weight of the dry gland was 3.78 grams and the average amount of iodine 0.004 grams (=4 mgm.) for the entire gland. The total maximum value of iodine was attained in individuals from forty five to fifty five years of age, viz. 0.007 grams (= 7 mgm.). It decreased rapidly during the next ten years to 0.003 grams (= 3 mgm.).

Zunz (75) in his studies on the chemical composition of the thyroid gland gives figures which seem to correspond most nearly

/ with mine .

with mine. He presents many analyses but the main facts are as follows.- The average weight of adult human thyroid is 26 to 30 gm. between ages nineteen and fifty five, but there is great variability. The water content also varies but approaches a mean of 75 to 76 % for all ages. There is always more iodine in the glands obtained from men between twenty five and fifty five than in glands of men of nineteen to twenty four. The average content of iodine in the fresh or dry gland tends to increase with the diminution in weight of the gland. The iodine content averaged 0.56 mgm. per gm. of fresh substance ( i.e. 1.68 mgm. per gm. dry, if the fresh gland has 75% water) from nineteen to forty four years; it increased gradually from 0.23 mgm. in heavy glands to 0.68 mgm. in glands of low weight. No difference in the iodine content of the two lobes was found.

Graham (76), in a study of the physiological activity of adenomata of the thyroid in relation to their iodine content, found the iodine content per milligram of dry gland of specimens used varied from 4.31 to 0.00, most being under 1.0. Incidentally it may be noted that he demonstrated by the tadpole method that adenomatous thyroid tissue had a similar effect to that of normal thyroid but was less active, the effect depending on the iodine content.

In studying the tables of my own findings as regards histological appearances and iodine content two things stand out clearly: one is the greater total weight of the operation goitre thyroids , especially when it is remembered that part of the gland was left behind, as compared with the majority of the post mortem thyroids, where the whole gland was examined: the other is the large number of "+" signs in the goitres as compared with the non-  
/ goitrous -

goitrous - in other words there is a much more complicated picture histologically in the goitres.

One difficulty I met quite early in the histological part of these studies was the extraordinary complexity of the pictures presented. Marine found the same thing, as before stated, and was driven to study fundamental changes as seen in animals or at autopsy. Likewise I have found it necessary to study and compare autopsy and animal thyroids, but in spite of that I have not found it possible to classify satisfactorily many goitre specimens on a histological basis only; for, in any one gland, even in one field, one can see all types of change - resting colloid, hyperplastic colloid, atrophy, adenoma, fibrosis and so on - even a cursory glance at the photomicrographs will show this. There are certain exceptions to this e.g. (4), D.B.1/1693 (Figs. 37, 38) which was clinically "exophthalmic" goitre and where the main appearance is hyperplastic, with this is a low iodine content both per gram and total; also (6) 1/1706 (Figs. 39, 40), another exophthalmic goitre case shows a uniform hyperplastic picture and ~~yet~~ its iodine content is about <sup>half</sup> ~~five times~~ that of the other.

In the clinically "Simple" group, numbers (9) 1/1762; (49) 1/2619; (Figs. 5, 8, 9.), conform to the "non-hyperplastic atoxic" type of Wilson and Kendall (loc. cit. 22). While the histological picture of these two cases is, in the main, similar the iodine content is much greater in (9), 1/1762 than in (49), 1/2619. The others of this same group have a more varied histological picture (Figs. 1, 2, 3, 4, 6, 7), including the presence of "adenomatous" areas, the iodine contents also are very variable.

In the clinically "Toxic, non-exophthalmic" group the presence of hyperplastic and "adenomatous" areas is seen in all, except (36), 1/2347 (Figs. 32, 33) where degeneration is a noticeable feature.

The iodine content per gram of this case is relatively high and the total amount of iodine in the gland is very high - 115.84 mgm.

It corresponds approximately to the "non-hyperplastic, toxic" group of Wilson and Kendall (loc. cit. 22) both histologically, chemically, and clinically.

(27), 1/2065, (Figs. 27, 28, 29, 30) shows the highest iodine content of all this group, viz 2.30 mgm. per gm. with a total of 142.47 mgm. Histologically it shows all the varieties of pathological change ordinarily found in goitres, and in amounts and proportions which make it very difficult to catalogue it under one heading alone.

If now the post mortem cases be studied the matter is simpler to some extent.

The first of this series, (24), 1/2013, (Figs. 45, 46), an infant of two months, shows the foetal type of gland, hyperplastic with no true colloid and a very small iodine content; corresponding to the early findings of Baumann (loc. cit. 46) and Pellegrini (loc. cit. 74). Further the gland is uniform in structure throughout and so can be placed under one heading histologically.

The next case, (29), 1/2110, (Figs. 47, 48), an infant of five months, with a thyroid rather less in weight has smaller iodine content and histologically gives the appearance of an atrophied or exhausted colloid thyroid; this case had a double hydronephrosis and terminal broncho-pneumonia.

X The third case, (14), 1/1853, (Figs. 49, 50), aged seven years, and the seventh case, (39), 1/442, (Figs. 55, 56), aged fifteen years, which were both anaesthetic deaths and showed the usual appearances of lymphatism, are remarkably similar. Both are mainly of hyperplastic type with little colloid and that mostly granular, both show marked congestion, and desquamation of epithelium of acini, and the weights and iodine contents are almost identical.

The fourth case, (18), 1/1924, (Figs. 52, 53), is an interesting contrast to these two. It was the case of a girl, aged nine years, an orphan, with extensive tuberculous disease of lungs and intestine, and toxic changes in the parenchymatous organs. The thyroid is of uniform colloid type but with relatively large acini showing projections - the "sprig-like projections" of Marine and Lenhart ( p.17, loc. cit. 28) - indicating a previous hyperplasia which has now reverted to colloid type. There is no histological evidence of "toxic" changes in the thyroid as compared with the liver or kidney, where there were "cloudy swelling" and "fatty" changes. For a child of this age the weight of the thyroid is too high, 33.0 gm., and the iodine content also unduly high. Pathologically one must regard this as a pure colloid type of goitre, a reversion from previous hyperplasia. Unfortunately no clinical details as to treatment were available so I am unable to say whether or not iodine had been used. This would have explained the condition found in the thyroid.

In the next case, (40), 1/2491, (Fig. 54), a boy the same age, nine years, is seen merely a normal thyroid exposed to an acute, virulent, infection - in this case a pneumococcal meningitis. There is congestion and oedema of the stroma, the acini have faint-  
/ staining colloid,

-staining colloid, the weight may be considered normal, and the iodine content within normal limits for the age.

Cases, (35), 1/2345, (Fig. 60) ; (13), 1/1852, (Fig. 62) ; (30), 1/2112, (Fig. 66) ; (56), 1/2786, (Fig. 67) ; (37), 1/2351, (Fig. 79) ; (28), 1/2070, (Fig. 82) ; (5), 1/1696, (Fig. 100), may be taken as average normal according to age.

The first two of these were sudden deaths by suicide in otherwise healthy, young, individuals, both showing mainly medium-sized colloid acini; the weights are within the figures referred to above, and, while the iodine contents are considerably different they may be taken as within normal limits. Case (30), 1/2112, (Fig. 66) is interesting. Histologically there is dense colloid in medium-sized acini of regular outline, but the iodine content is unusually high, indeed the highest of this series, 6.10 mgm. per gm. and 28.30 mgm. in the whole gland. It was a case of cerebral tumour with decompression operation which went septic. Iodine was applied for a considerable period and it is reasonable to ascribe the high content to this fact in view of the numerous observations on the increase of iodine content following iodine administration. Case (37), 1/2351, (Fig. 79), is a medium-sized normal gland, showing some atrophied acini balanced by enlarged colloid acini. Case (28), 1/2070, (Fig. 82), is a small normal gland, but the patient was aged fifty and was bedridden for a considerable time. Case (5), 1/1696, (Fig. 100), is a large, uniformly colloid gland in a woman aged sixty, with iodine content average in amount.

Case (44), 1/2550, (Fig. 85), shows only an average gland, although there were well marked syphilitic lesions elsewhere and a positive

Wassermann. Anatomically and chemically the thyroid has not suffered especially from this infection.

Case (45), 1/2583, (Fig. 57), a girl of nineteen years, though dying from broncho-pneumonia shows little acute damage to the thyroid which is of uniform colloid type.

The adjacent case, (64), 1/2959, (Figs. 58, 59), of a young woman, aged nineteen, dying more slowly from carcinoma of ovary with extension to the peritoneum has a small colloid thyroid, with some slight hyperplastic colloid areas (Fig. 59), but a relatively high iodine content and no evidence of special injury from her malady, unless one accepts the slight hyperplasia seen as evidence of it.

Case (61), 1/2949, (Fig. 63), is really a small colloid goitre with evidence of previous hyperplasia (Fig. 63) as in case (18), 1/1924, (Fig. 53), and with small, atrophied acini. It is a gland which has reached a balance by involution to colloid from previous hyperplasia and in which the iodine per gram. and total iodine are relatively high.

Case (50), 1/2631, (Fig. 61) also might be classified anatomically as a goitre: there was a localised colloid nodule ("adenoma") in one lobe and both atrophic and hyperplastic colloid changes are present (Fig. 61). Though the weight is rather high (40 grams), the iodine content is not abnormal (0.93 mgm. and 8.63 mgm.)

Other examples of goitre, more pronounced anatomically though clinically there were no symptoms, occur in cases.- (60), 1/2918; (25), 1/2029; (46), 1/2586; (54), 1/2744; (51), 1/2692; (12), 1/1812; (26), 1/2032; (19), 1/1936. See Figs. 64, 77, 78, 86, 87, 88, 91, 92, 93, 94, 96, 97, 98, 101, 102, 103, 104, 112, 113, 114.

Examination of these figures and of the detailed descriptions

/of the

of the detailed descriptions of the thyroids (Appendix N ) will show appearances identical with the goitre cases showing symptoms and treated surgically. The iodine contents, however, do not reach the high figures shown in the operation specimens and the majority are well within normal limits. Thus, in case (60),1/2918 the thyroid weighed 137 grams with a low iodine per gram (0.67 mgm.) and only moderate total content (21.29) as compared with the case referred to above, (30),1/2112, with a weight of 20 gm. but iodine content of 6.10 mgm. per gm. and 28.30 mgm. total.

Several of these show "Adenomata", ( Figs. 78, 86, 87, 97, 101, 102, 104, 112, 114. ), either of "foetal" or "adult" type, with the usual appearances and secondary changes as previously detailed.

Case (54),1/2744), from a man aged fifty four , dying of diabetes and gangrene of the finger, has a thyroid of only 17.5 gm. and iodine content well within normal and yet there are very extensive pathological changes in the gland . Portions have been destroyed and replaced by scar (Fig.93), other portions show hyperplastic colloid. In this scar area (Fig.93) an interesting appearance of closely packed,hyperplastic, epithelium is seen suggesting a "foetal adenoma" and yet it is more reasonable to regard this as merely an attempt at regeneration from surviving epithelium of the damaged area. There has been previous haemorrhage in this part (Figs. 93, 94.) - a frequent association and probable precursor of many of such scarred patches, as before described.

In (51),1/2692, (Figs. 96, 97, 98 ), a woman of fifty five with carcinoma of the cervix to which radium had been applied, the histological appearances are mainly atrophic and degenerative while

/ the iodine

the iodine is markedly low - only 0.08 mgm. per gm. and 1.83 mgm. in the whole gland.- Whether this atrophy and exhaustion is to be ascribed to the radium or merely to the long-standing malignant condition I am unable to say and merely record the fact.

Some cases especially among patients of more advanced years show less striking histological changes, but, taken along with the total weight they indicate unusual thyroid enlargement - goitres anatomically though not clinically. Thus,

(58), 1/2864, (Fig. 99) has considerable hyperplasia throughout with an average iodine content. (1), 1/1640, (Fig. 108) and (23), 1/1994, (Fig. 109) might perhaps be regarded as in the upper limits of normal colloid glands but the large size of the colloid acini and the weights of the total thyroids incline one rather to place them as simple goitres of uniform colloid type, the result of previous hyperplasia, with relatively high iodine content.

Case (57), 1/2810, (Fig. 116) was that of an old woman of seventy four, who died from cerebral haemorrhage. The thyroid is an atrophied colloid gland with "colloid cysts". These might quite reasonably be regarded as "adenomata" having compressed, atrophied acini around them as a "capsule". When that amount of atrophy is remembered the weight of the gland, 59.0 gm., which represents mainly the large colloid acini, indicates the degree of hyperplasia that has occurred. This hyperplasia has reverted largely to colloid with corresponding iodine content.

The other cases shown on the tables (Appendix K) call for no special comment, except (63), 1/2993, (Figs. 72, 73, 74, 75.), a fatal case of acute exophthalmic goitre in a man aged forty five,

/ who rapidly

who rapidly emaciated and died, having, towards the end, acute enteritis. The thyroid, which was considerably enlarged and weighed 84.0 grams, is for the most part hyperplastic, with exhausted, atrophied areas, and old and recent haemorrhage. The iodine per gram is low, 0.7 mgm., as is to be expected with this type of epithelial change, but the total amount is considerable, 14.61 mgm. The whole picture is that of a gland driven to exhaustion and illustrates one mode - fortunately not a common one - of natural termination of this type of thyroid activity. That there has been previous damage is seen in the older scarred areas, and the process of formation of scar is seen (Fig.75) in parts where the epithelium is undergoing disintegration.

In the foregoing study no attempt has been made to find the distributiob of iodine in the several parts of the thyroid, although this information is desirable for the full understanding of iodine circulation ( and, inferentially, of hormone distribution). Information on this point is furnished by Tatum (77) who showed that, in thyroids of cattle, sheep, and pigs less than 40% of the iodine existed in the cells, the remainder being in the colloid. Van Dyke (78), using Tatum's method, showed the ratio to be fairly constant despite variations in morphology and iodine content of glands examined. He also showed that the ratio value for dog's thyroid was much lower than in the case of cattle or sheep, while human thyroid lay between these two groups. Baumann considered that the iodine lay only in the colloid.

In order to compare these findings in

/ human cases



human cases with what obtains in animals several series of sheep thyroid were examined. These thyroids were obtained fresh from the abattoirs immediately after the animals were slaughtered and treated in the same way as the human material except that a number of glands were pooled for chemical examination. The individual glands, or pieces of gland, all gave the same histological picture and the glands varied but little in size or shape: they can thus be regarded as average samples of normal sheep glands.

As figs. 151, 152, and 153 show, the acini are regular in shape, size, character of epithelium, and colloid content; also the iodine contents (Appendix K, Nos. A,B,C,D.) are very even and higher than the average of human glands. The figures given by Marine and Lenhart (Loc. cit. 29) for colloid sheep thyroids are from 3.691 to 1.769 mgm. per gm. dry gland. Numbers A and B (3.85 mgm. and 3.60 mgm. respectively) were from sheep killed at the end of November, i.e. early summer, and show a slightly lower content than those killed in the beginning of July, i.e. mid winter, (Numbers C and D, 4.61 mgm. and 4.63 mgm. respectively). The numbers examined are too small to generalise upon but they suggest only a very slight variation between winter and summer-killed animals. Such variation has been described by Fenger (79), and Seidall and Fenger (80), in thousands of thyroids received at Chicago noted such variation in cattle and sheep, but less in pigs.

These observers show that there is, in general, from two to three times as much iodine present in glands in the months between June and November (i.e. summer and autumn) as in the months between December and May (i.e. winter and spring). They conclude that temperature is the most important factor in the production of this

/ variation.

variation. Mills (81) has shown, experimentally, in animals that high temperature causes diminished activity - as judged by morphology - and low temperature increased activity.

In New Zealand the temperature variations are, generally speaking, less than in the United States of America, which may account for the little difference in the few examined. This is a matter, however, which requires further investigation. I am not aware of the conditions of winter feeding of sheep and cattle in the United States, but in New Zealand both can, in most places, be wintered outside, which means that their diet is relatively constant.

In this section the general subject has been advanced a stage further. Without discussing the pathology in detail at present it is obvious that the goitres examined in New Zealand conform to those described elsewhere, more particularly in America, that the general relationships of iodine content, structure, and clinical features are similar to those noted by other observers. Further, from examination of post mortem material it is obvious that thyroids that can be regarded as quite normal are relatively few. A state of affairs also recorded by Simpson (82) in routine examinations at the State Institute for the study of malignant disease, Buffalo, New York. He found adenomata in 80% of 200 consecutive post mortems in the Buffalo area and he quotes Aschoff as saying in his lectures that he could find adenomata in the thyroid gland in every individual who came to autopsy from the region of Freiburg in Breisgau.

Having established the facts that the goitres are of well recognised forms and that there are many abnormal thyroids to be found in autopsy material, it is necessary to examine certain other factors that may have a bearing on the causation of these abnormal conditions.

## VI. IODINE CONTENT OF SOILS AND FOOD STUFFS .

See Appendix L, and Maps.

While a considerable amount of literature has accumulated on the question of the iodine content of food stuffs I have not been able to get much detailed information in the literature at my disposal as to the iodine content of soils.

It is true sporadic observations have been made but, as will be shown later, these may be misleading.

Richet (82, a) quotes Chatin and Gautier as saying that iodine is present in small amounts in almost all geological beds of the earth, igneous rocks containing more than sedimentary - that this obtains also to some extent in New Zealand will be shown graphically later - while chalk and magnesium contain very little.

Clarke (83) regards iodine as the least abundant of the halogen group, being limited to certain springs and minerals and present generally in sea water and sea plants.

Hayhurst (84) in a most interesting paper on "The present-day sources of common salt in relation to health, and specially to Iodine Scarcity and Goitre" gives the results of observations on the iodine content of the common salt of America. He shows how the much greater solubility of iodides leads to their loss in the mother-liquor in the process of crystallising out common salt (sodium chloride) either in the salt industry or in nature during the slow drying up of sea beds and formation of rock salt deposits. He cites Abel and Halla as saying, "The sea is the great store house of iodine", hence sea plants contain relatively / large amounts

large amounts and on their disintegration the iodine is returned to the sea. Hayhurst sums up the matter thus.- " The practical significance of this (the erratic distribution of iodine on the earth ) can be stated in one short sentence. The land surface and, indeed, salt (sodium chloride) deposits and inland salt brines cannot be depended upon for iodine; that which was once present has been virtually leached out and all washed away into the sea, or, at least into lower lying plains or deeper earthy strata. Naturally this condition is progressive. It accounts for the tendency in wild animals to favour certain salt springs or 'licks' and to quit them for others without apparent cause. Kalkus (85) reports that 'deer lick' soils showed an iodine content of 0.032% whereas soils from a goitrous district showed only 0.0015% to 0.00161% (= 161 in 10<sup>7</sup>). Civilisation augments the depletion process, for, as long pointed out by soil economists, plants remove salts from the soil for the use of animals whose wastes we cause to be deposited in 'pockets' or drainage systems which lead to the sea, and not back to the soil. "

Examination of the iodine content of food stuffs

Examination of the iodine content of food stuffs has been made by Forbes and Beigle (86) who give the results of 878 analyses and they state that garden vegetables and the cereals furnish most of the iodine in the human dietary. They say that foods from localities in which goitre is of frequent occurrence show neither excess nor deficiency of iodine.

Bohn (87), using Kendall's method for iodine (88), got results on the whole in agreement with those of Forbes and Beigle. He found no iodine in the great majority of food stuffs analysed and only traces in the remainder. The conclusion reached is that

/ the iodine

the iodine requirements of animals are satisfied by the small traces of that element which occur in the food stuffs of vegetable origin, such traces of iodine being accidental and not in any way connected with the nutritive processes of the plants themselves.

The distribution of iodine in certain plants and animals tissues examined by Cameron (Loc. cit. 66) has already been referred to.

Richet (Loc. cit. 82) gives the iodine content of sea plants as 0.001 to 0.7 per cent of the dry tissue, and states that fresh-water plants contain much less according to the water in which they grow: ordinary land plants contain even less. He also states that the iodine content of French wines varies, those of Champagne containing none while those of Macon are relatively rich.

The work which Richet quotes was done a number of years ago and one is a little doubtful of the accuracy of his findings in view of the difficulty experienced by us in analysing small amounts of iodine in vegetables at Otago University..

The first attempt to estimate iodine in plant material in my laboratory was that by Hicks and myself on sea weed, and as noted, we found 0.10 mgm. per gram dry weight. Later we attempted to estimate the iodine in soils and food stuffs, using Hunter's method. Mrs. C.E.Hercus, B.Sc., working with Hicks, tried various modifications of the method in a systematic examination of vegetables but the results were not satisfactory. This part of the combined investigation into goitre has been held up temporarily but will be shortly resumed thanks to a grant from the Health Department and chemical workers in the persons of Messrs  
C.L.

/C.L.Carter, M.Sc., A.I.C

C.L.Carter, M.Sc., A.I.C. and F.H.McDowall, M.Sc., A.I.C., of the staff in the Chemistry Department of Professor Inglis of Otago University.

Only at the end of 1923 did I become aware of the work of von Fellenberg. This work fills the gap as to the distribution of iodine in nature and in food stuffs and will form a basis for comparison when we get our New Zealand figures. It also furnishes a method which we have not so far applied to food stuffs.

Von Fellenberg confirms a number of Chatin's earlier observations as to the occurrence of iodine but he does not agree with him that the iodine of the air can be a preventative of goitre for the air contains extraordinary little ( $4 \times 10^{-8}$  gm. per cub. m.). He supports Chatin in his conclusion - that goitre and cretinism were brought about through the lack of iodine content in nourishment, as well as prevented by sufficient addition of iodine and his statements in support of this are:-

" In general we find in any like or analagous vegetables La Chaux de Fonds has more iodine than Signau. Some exceptions are present. Lettuce from Signau contains more iodine than a related vegetable from La Chaux de Fonds. In rhubarb leaves we find also the distinction in the same way, while in the stems normal relations hold. In all other cases, in the products of La Chaux de Fonds more iodine is found. This appears all the more striking as La Chaux de Fonds (1000 metres above the sea level) is 300 metres higher than Signau (700 metres). "

	<u>La Chaux de Fonds.</u>	<u>Signau.</u>
Cabbage	--	27
Lettuce	18	--
Cut Mangols	15	10
Carrots	7	5
Red Cabbages	61	21
Peeled Potatoes	7	4
Unpeeled Potatoes	18	11
Rhubarb Stems	10	3
Rhubarb Leaves	21	28
Apples (Cored)	6	1
Apples (Uncored)	7	2
Apple Cores	32	19
Milk	9	3
Drinking Water	1.40	0.067
Frost	47	80

/And

And we then see that the air in the higher region is poorer in iodine than in the lower region, and that also precipitation brings less iodine.

One might think our results are accidental -- perhaps one has been manured more with iodine-containing manure; but, however, we see an immense difference in the iodine content of drinking water, on which also the difference in the vegetables must rest. The water of La Chaux de Fonds contains 21 times more iodine than that of Signau. So also the earth and the rocks on the Jura Mountains are consequently richer in iodine than in the Emmen Valley. The difference must make itself operative during the period of growth. ....

La Chaux de Fonds is almost free from goitre while Signau is distinctly goiterous.

The figures refer to what V. Fellenberg calls micrograms (= 1 millionth gram or 1 part in  $10^6$  parts).

(Note - Our N.Z. figures are in parts pr. 10 million or  $10^7$ ).

A comparison is also given of an average daily intake of iodine in these two areas :-

		<u>Microgram 12 per Kg. fresh substance.</u>	
		<u>La Chaux de Fonds.</u>	<u>Signau</u>
		(almost free from goitre)	(goitres)
300 gm	Bread	4.9	2.4
500 gm	Potatoes	3.5	2.0
300 gm	Vegetables, average of lettuce, mangold, cabbage, red beet, rhubarb.	4.2	3.1
1.5 litre	Milk, in which butter & cheese are included	13.5	4.5
300 gm	Apples or other fruit	1.8	.3
60 gm	Fat	0.6	0.6
2 litres	Water, used for cooking	2.8	0.1
10 gr.	cooking salt	.0	.0
	TOTAL	<u>31.3</u>	<u>13.0</u>

Figures for common food stuffs are also worth referring

to :- " vegetable & fruit 2-30.  
 Tropical fruits 5 - 136.  
 Wheat from various sources 2-19  
 Milk, eggs, meat 5 - 106.  
 Arachis oil 4,  
 Lard 17,  
 Cod-Liver-oil refined 7200, crude 3370.  
 Aquatic plants 182 - 448.  
 Dried seaweed about 900,000.  
 Fishes 29 - 163. "

These are many other interesting observations in this work, e.g. the iodine from coal, iodine in air at different levels, etc., <sup>but</sup> enough has been quoted for the present needs of this study.

The investigation of soils in New Zealand as to their iodine content has proceeded more satisfactory. This work was begun in a minor way in my department by Hicks and myself but owing to press of other matters and need for subdivision of the goitre researches it was handed on to Mr. Carter working under Professor Inglis direction. Professor Hercus being likewise interested in this side of the work circularised the various health officers and inspectors in both North & South Islands with the result that specimens have come to hand in relatively large numbers. In order to concentrate the work it seemed desirable to have more detailed observations on areas known to <sup>be</sup> more or less endemic for goitre and also areas accessible to Dunedin in order to facilitate observations and the collection of samples.

While I personally have collected samples along certain routes I lay no claim to the laborious chemical work that their examination has entailed. That has been done by Mr. Carter & Mr. McDowall and as I hope to be able to refer to a published paper by them on this subject shortly I shall not anticipate it by

detailing/

more than to say that it is a modification of Baumann's colorimetric method detailing their method - the iodine being liberated in solution by "nitrosulphuric" acid and concentrated by shaking with carbon disulphide. After many trials and failures they achieved a method of analysis giving wonderfully accurate results with minute amounts of iodine in soil. The same method, unfortunately, was not so satisfactory for minute amounts of iodine in vegetable tissues.

The samples of soil were collected in dry, clean tins, labelled and sent to the chemical laboratory. The chemist did not know the condition of the areas as regards goitre or geological formation. These facts were collected independently.

#### VII. COMPARISON OF IODINE CONTENT OF SOIL, GEOGRAPHICAL AND GEOLOGICAL RELATIONSHIPS, AND DISTRIBUTION OF GOITRE.

The results of these analysis appear in appendix "L" Merely looking over the figures and the places to which they refer gives but little information without some graphic presentation. Accordingly, I have made a series of maps showing iodine content of soils and goitre incidence in school children. The small North & South Island Maps are on the same scale and superimposed upon the geological survey maps so that the relation of geological formation, iodine content, and goitre incidence in school children can be seen at a glance.

In view of the fact that the adult population is more migratory, and therefore likely to be less influenced by any one locality, it seemed more rational to compare the iodine content of soils with the incidence of goitre in school children, most of whom have been brought up in the locality. That the school figures correspond wonderfully with the hospital and other statistics as regards geographical distribution will be evident

if they are compared.

The Maps are as follows :-

1. A general place Map of New Zealand to show areas where iodine in soil was estimated (black rings), and school areas where goitre incidence was noted.

This Map is on same scale as Nos. 2 & 3 and is merely presented as a general guide to localities.

2. North Island, (a) Geological survey map with (b) Iodine content of soil in circles marked & coloured. (c) Goitre incidence in school children in circles marked and coloured.

3. South Island, (a), (b) & (c) as in 2.

4. Map of North, Central, and South Otago, on larger scale. To show iodine content of soils, in small coloured circles and goitre incidence in school children, in large coloured circles.

5. Map of Dunedin, on still larger scale.

To show iodine content of soils, in small coloured circles, and goitre incidence among school children, in large coloured circles.

Note: The colours have been so arranged that low iodine content is the same colour as high goitre incidence and vice versa. In that way it was hoped that, if there was any correspondence between low iodine and high goitre the colours would likewise correspond. To what extent that occurs will be seen and will be discussed. The actual figures for iodine, in parts per  $10^7$ , and for goitre incidence per cent, are put in the respective circles.

Map No.1 need not be further referred to except by anyone unfamiliar with the general geography of the country.

Map No.2 (a) shows at a glance the general geological formation of the North Island of N.Z.

Unfortunately the iodine examinations are, as yet, small in number, but it will be seen, in 2 (b) that in the Mount Egmont (New Plymouth) district, which is largely volcanic, there are high iodine figures, while Wanganui, Fielding, etc., show low content. Lower Hutt (near Wellington) is variable, Aramote, near Wanganui, also variable, while Rotaruru - North west of Rotorua - ranges from 1 to 170. Auckland, where more samples were taken ranges from 10 to 256, the high figures are from the volcanic soils, especially Mount Eden.

If now, in 2 (c), the goitre incidence be compared certain correspondences occur, thus New Plymouth area is free of goitre - and so red coincides with red on the maps (b) & (a) - Wanganui approximates in colours, also Lower Hutt. Auckland is low in goitre, Martinborough (near Wellington) is low in goitre (red) while the iodine figure is also low (green).

This map, therefore, is in no way convincing as regards any correspondence of low iodine and high goitre. Incidentally the number of places examined for goitre in schools is much greater than the number of places for iodine content, but it serves in that way as a guide for further work.

Map No. 3., the South Island of New Zealand, on the same lines as the preceding has more figures both for iodine and goitre incidence.

Banks Peninsula, which is volcanic, and corresponds geologically with Mount Egmont in the North Island had not, at the

time of writing been examined, but many samples have been examined from the city of Christchurch and adjacent townships. It will be seen that the figures are uniformly low, mostly below 10.

The same applies to the Timaru area, where the iodine ranges from 1 to 6, and Waimati, a little further South, shows but 1. If the geological map 3 (a) be compared with 3 (b) it will be seen that from Rangiora, North of Christchurch, to the Waitaki river, South of Waimati, is sedimentary deposit forming the great Canterbury plains. Across these run numerous rivers, including the large rivers Waimakariri, Rakaia, Rangitata & Waitaki.

At Timaru is a small, old volcanic area geologically, but in spite of that the iodine is low, so far as the present samples have shown.

If the goitre incidence of the same area be compared a remarkable correspondence in colour is seen, i.e. a high goitre incidence, but curious patches of low incidence appear; thus in the midst of the green circle at Christchurch occurs the brown circle (14%) of Heathcote. In this suburb of Christchurch Hercus (loc.cit.8.) has shown that the water supply is contaminated slightly with sea water and shows a higher saline content (the iodine has not yet been examined) while the rest of Christchurch is supplied mainly by art<sup>s</sup>isan water of great purity both chemically and bacteriologically.

The iodine figures for Nelson & Marlborough districts are low though the geological formation varies somewhat but there is considerable sedimentary deposit in parts here - not clearly shown in so small a scale map.

There/

There are no detailed goitre figures as yet for these districts, but I have had personal communications from medical men in Nelson to say that goitre is prevalent there.

On the west coast the iodine is low and the formation largely sedimentary. Some of the samples were taken from what were probably raised beaches. At Kumara & Reefton, more inland, higher figures occurred.

The goitre incidence colours in the main correspond, the figures being high even at Reefton where a slightly higher iodine was found.

Further south low iodine figures - and the green circles - predominate, with outcrops of higher figures e.g. in Dunedin. Geologically the areas examined are mainly sedimentary and percolated by rivers. Thus the Taieri plain, south of Dunedin, washed by the Taieri river; the Clutha, or Molyneux, valley and its delta, by the Great Clutha; the Manuherikia plain by the river of the same name; and, in the south, the Oreti and Aparima rivers drain the surrounding flat country.

There are volcanic outcrops at Dunedin which might be expected to be associated with high iodine as in the New Plymouth area, but the populated and cultivated parts are covered with clay or deposit washed down from the hills and, in actual fact, the high iodine figures were obtained in a low lying area as will be shown in the detailed map.

The goitre figures and colours show a striking correspondence in the Taieri plain and along the Clutha valley & mouth, but in the Manuherikia plain and in the Southland area (Invercargill & surrounding country) the goitre incidence is less than the iodine figures would suggest - assuming they should run

parallel/

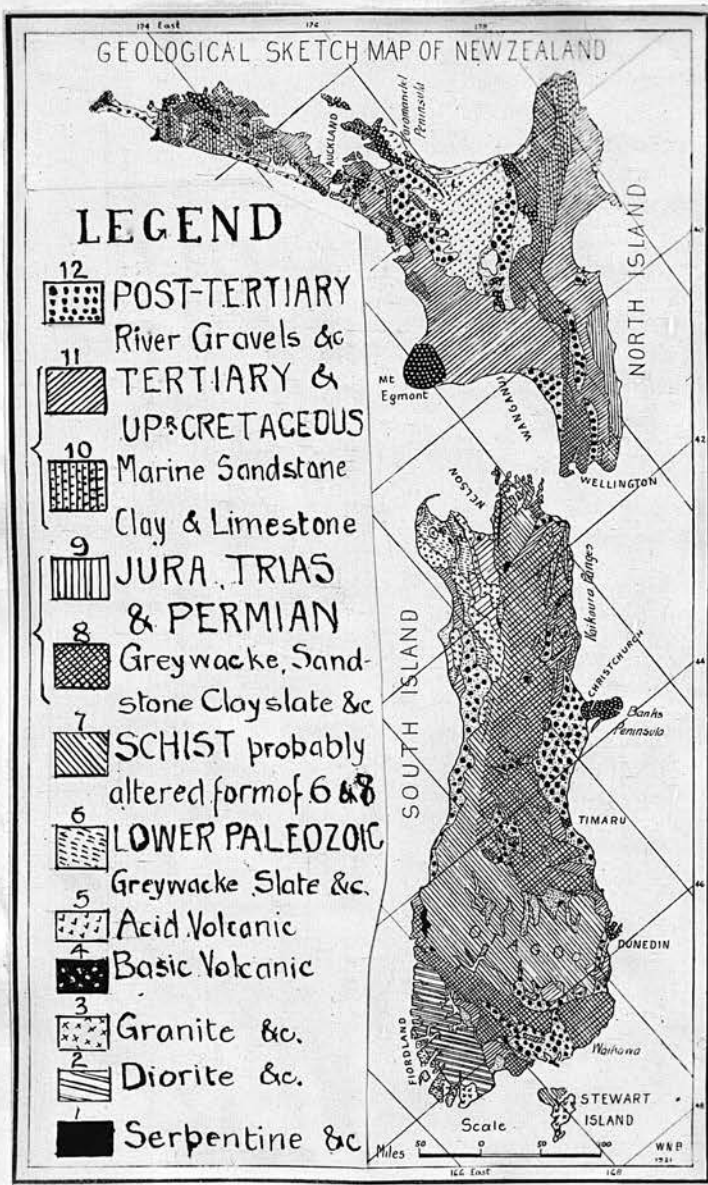
parallel.

In the more detailed maps described below possible explanations for these discrepancies will be seen.

So far as the relation of iodine to geological formation is concerned it may be stated generally that sedimentary deposits, washed or "leached" out by rivers, are low in iodine content. This is to be expected from the solubility of the iodides as already pointed out by Hayhurst (loc.cit.84). Certain volcanic areas, e.g. Mount Egmont (New Plymouth), and part of Auckland, are high in iodine and also areas soaked by sea water. Where the high iodine content for Dunedin occurs is in a small patch of flat land, formerly marsh and permeated by the sea but now drained and reclaimed. No river leeches this part, nor is it readily washed out by flood water from the higher levels.

When a more detailed examination of any area is made there are seen numerous patches relatively rich in iodine, sometimes with surrounding areas poor in iodine, which cannot be satisfactorily explained by any general geological map. Such areas of greater iodine may be due to minor faults, or pockets not subjected to any washing out process.

I anticipate that the relations of Iodine occurrence to geological formation in N.Z. will be considered in greater detail by my colleague, Dr. Benson, Professor of Geology at this University, and I am indebted to him for a copy of his work on the Geology of N.Z. A photograph of the map in which is here appended with a recently amended legend by Dr. Benson. This small map taken along with the larger maps gives fuller information as to the geological nature of the various areas.



Map, No.4., of North, Central & South Otago on a larger scale to the preceding maps, shows, in greater detail the iodine and goitre figures. Here again this form of presentation serves to show gaps requiring filling, especially further iodine figures in many of the school areas.

In the area just South of the Waitaki - extending N.W. from Oamaru - the iodine figures available vary considerably. In Oamaru itself they range from 2 to 34; while some forty miles further up the river at Kurow, 50 is reached, with intermediate findings of 0,4,5,10.

At Kurow a very interesting observation was made by a student and friend of Mr. Carter's, who had sent samples of soil to Dunedin. He noticed that some sheep ignored the piece of "Salt lick" put out for them and went a considerable distance to a certain clay bank in order to lick the clay there. On a sample of this being examined it was found to contain 50 parts per  $10^7$  of iodine. Clay from alongside a creek in the neighbourhood had 0 parts, while the "Salt lick" - which is an imported article - contained 14 parts per  $10^7$ . A similar action on the part of wild animals is mentioned by Hayhurst (loc.cit.84).

The goitre incidence in this area is variable but on the whole low, and the explanation probably lies in various other, as yet uncharted, patches of iodine in the soil.

Further South, along the Shag river, iodine figures for Palmerston, and Dunback - some ten miles further up this river - are 4 to 10 parts. The soil here is clay and river detritus.

The goitre figures are moderate - 25% at Palmerston to 16.6% at Dunback.

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South of Palmerston there are no iodine figures available but the school figures are moderate to low, with one small higher area at Mount Cargill, viz. 27.7.

The Dunedin figures will be fully considered in the next map and only the general school figure is put in here, viz., 17%, with 18.4% in the Peninsula schools across from Dunedin harbour.

The Taieri river area in its upper reaches has not been tapped as yet for soil samples so no iodine figures are available. The goitre incidence is variable but moderate on the whole with a higher patch (50%) at Patearoa a gold mining settlement.

In the Maniototo plains (on which are the townships Naseby, Ranfurly) only the iodine content at Naseby has been examined and found to be 6.

The goitre incidence here is fairly low, Naseby itself having 15%, and Wedderburn only 7.6%. This area requires more detailed examination for iodine content. Naseby was probably the worst place to take a sample from as the inhabitants grow few vegetables and the soil in and around this township has been literally washed out by the sluicing for gold, carried on there formerly to a large extent but now almost abandoned. The result is still seen in the silt and stones and in the furrows and clefts of old workings. A similar state of affairs is seen at St. Bathans - in the upper part of the Manuherikia valley - (see top green circle in centre of map 4). Here no iodine figure is available but the goitre figure is high - 45.4%.

Further down the Manuherikia valley soil/samples at Lauder and Chatto Creek were negative for iodine. This is an area of rolling downs with flats along the river, The sample at Lauder

was/

was taken from a garden on a flat, sometimes flooded after rain, while the Chatto Creek sample was from higher ground.

The School figures vary, generally higher on the flats and lower on the ground away from the river, but the average figure is moderate compared to those of the Clutha valley.

As in so many other parts further samples are necessary here before it can be said that there is no correspondence with the goitre figures.

At Alexandra the Mamherikia joins the Clutha, or Molyneux.

If the Clutha be followed from one of its sources, viz. Lakes Hawea & Wanaka (see top left of Map 4), to its mouth a definite line of endemic goitre is revealed - as judged by the school figures.

The iodine content at Lake Hawea is low - 2 parts. The next site so far examined along this line is Alexandra where the figures range from 0 to 7 and up, to 24.

Then comes a long gap in iodines until the lower end is reached and here a more extended examination has been made with instructive results.

The School goitre figures are much more complete and show as a preponderance of green circles as far as Ettrick (middle of left side of Map 4) where the high figure of 62.5% occurs. Millers Flat, the blue circle beside Ettrick, is on the opposite side of the river. From Beaumont the river runs through a gorge and there are only isolated houses until Balclutha is reached. The clusters of circles to right and left of the Clutha river mark schools along the Pomahaka river, to the left, and small tributaries/

tributaries of the Clutha to the right. The goitre incidence of these areas is low to medium, an exception being Waitahuna diggings area with 58%. The conditions here approximate to those of St. Bathans and Naseby above described.

In the Balclutha, Inch Clutha, Stirling & Kaitangata area - all within ten or fifteen miles of each other - both circles are green. The iodine content nowhere rose higher than 10 and that only in the part of Balclutha, known as Rosebank, some distance above the river. Other samples gave, from 0 to 2 & 4 parts iodine. Water from the Clutha river, at Balclutha, showed no iodine in 900 million parts.

School goitres in these places run to high figures.

51, 56, 61, 65, and even 72 per cent.

This indeed is an endemic area and one worth more concentrated study.

As mentioned in the introduction to this thesis I quite accidentally learnt of the occurrence of goitre among sheep in this area. Near Stirling lives a Mr. Anderson, a farmer and breeder of prize sheep. To him and his daughter, formerly a student of mine, I am indebted for the descriptions of the conditions found.

It appears that in the Spring of 1917 many sheep produced feeble lambs, hairless and maldeveloped, with large goitres and pink hoofs. Such lambs were usually born dead and had huge thyroids dark red in colour and sometimes ruptured at birth. The ewes were stud ewes, fed artificially through the winter -- their gestation period - on crushed oats, chaff & linseed cake.

This information I got in 1918 too late to attempt any trial of the effect of iodine on these animals that year,

but/

but in the Winter of 1919 Mr. Anderson called upon me and I arranged with him to try the effect of iodine on six "High fed" ewes. The stud stock was divided into (1) High feed - 2 meals a day of oil cake, bran, peas, oaten chaff, grass in paddock, rock salt, turnip, and no water. (2) Medium feed - more grass and less above. (3) Normal feed - grass in paddock and turnips.

The manure on the land is partly artificial, the oil cake is partly of N.Z. origin and partly imported.

It was suggested to Mr. Anderson that he feed 6 "high feed" ewes with .023 gm. <sup>KI</sup> per day, per ewe, mixed with the feed during the gestation period, (the K I in sufficient amount was mixed with the total feed and this divided so as to give approximately the amount stated to each ewe.) Six "high feed" ewes were to be kept as controls on the usual feed without addition of iodine.

At the end of 1919 Mr. Anderson reported that no goiterous lambs were born either among those not treated or those treated with iodine. It appeared, however, that the controls had had some extra green feed, the K I treated cases were on exactly the same feed as previously when goiterous lambs had been born.

The experiment was therefore inconclusive.

At the end of 1920 Mr. Anderson again reported. This season no K I had been given but all the ewes got green feed and water except one which was kept on oil cake and dry feed, getting turnips as its only source of water. This ewe had a lamb with large goitre, poor fleece and large ears. All the other ewes had normal lambs.

From this period to the end of 1923 I did not hear from Mr. Anderson and other matters prevented my visiting this district.

but/

But at the end of last year I learnt that goitres were still occurring occasionally, not only in sheep but also in calves. When our methods for estimating iodine in vegetables and food-stuffs are established we hope to resume work in this area.

To resume the iodine contents and school goitres.

North-east from Balclutha is a flat stretch of country in which are Tuakitoto and Milton, both with low iodine content and medium to high goitre indices.

Going further north east the next group of circles are on the Taieri plain, a flat stretch of fertile country and one of the earlier settlements of this part. The Taieri river runs through it, bringing down a large amount of fine silt, the most of which comes from gold dredging in the upper reaches. After rains this plain is frequently flooded. The river water gave only 1 part per 950 million.

The iodine figures are low - and many samples have been taken from different parts - ranging from 2 to 7 with slightly higher figures, 14 & 16, on the higher ground adjoining the plain.

The school goitre figures are limited to the Mosgeil area and are moderate - 25.6%.

Map No.5: This shows, on a larger scale still, a much more detailed study of iodine content and school goitre incidence.

The sizes of circle and colours are the same as in the previous map.

As the small scale map (No.3(c)) indicated a considerable range of iodine figures is found.

The three red circles - iodine contents 136 to 182 are over what was formerly sea-marsh land, and where, at one time, the

sea must have come through into Otago harbour. It is now reclaimed and thickly populated. Within a few chains of the 150 red circle is a green one, indicating 0 iodine. This was a patch of bituminous clay which, neither on the surface nor ten feet deep, where blue clay occurred, was iodine estimable. On either side of this are purple circles, indicating 34 & 38 parts iodine. Further down in sand hills of the cemetery only 2 parts occurred and above Anderson's Bay, on higher ground (lower border of map) adjacent samples varied considerably, from 8 to 36.

Still on the same side of the Map, in the other (south west) end of St. Kilda district the figures range from 15 to 36. Circles with 15 & 36 (dark green & purple) indicate the site of large vegetable gardens cultivated mainly by Chinese for market purposes.

The Schools in this area show medium figures for goitre, rather higher at St. Clair (23%) and Anderson's Bay (24.6)

The iodine figures for the hill suburbs, Morningson, Roslyn, and Maeri Hill vary from low to medium - 10, 14, 16, to 30, 33, 36, and reference to the detailed figures and soils will show that the same type of geological formation may have varying amounts of iodine, e.g. brown loam, basaltic in Bellknoves has 33 parts & the same type of soil in Morningson North showed only 14 parts.

The Schools in this area show as two purple and two brown circles - 11.7 to 22.5%.

Further over, in the Kaikorai valley - along the Kaikorai stream - the iodine figure is 14 and the school largely serving that area shows 23% goitres. At the top right appears a blue circle round Waikari school with 32.5% goitres. This school is on the outskirts and serves largely children coming in from the

country/

country around. More to the middle right in the map is the Maori Hill and town belt area with lower iodine figures on the whole, 10, 10, 12, 14, with a 25 circle close to the Maori Hill school itself. From this area - at my own residence - the first soil samples were taken. I tried the effect of watering a small patch in my own garden once in three weeks with 1 gm of K I dissolved in one pint of water. The object was to see if turnips in this patch would show higher iodine than those in a central patch not so watered. As before explained the examination of vegetables for such small amounts as occur in them was not successful, the results being too near the experimental error to be satisfactory. This part of the experiment therefore failed, but soil samples taken from the watered area - three weeks after the previous watering - showed a slightly higher iodine viz., 30 parts. The goitre figure for the Maori Hill school is relatively low - 12.7%.

Continuing to the right of the map from the previous area one comes into a narrow valley, that of the Leith stream. Iodine estimations on the water of this gave 2 parts per 900 million - more than twice that of the Taieri river. Soil samples from gardens along the river valley gave rather low figures 2, 8, & 18, a sample from the high ground above the right bank showed 12 and one from Dalmore - high ground rising steeply on the left bank gave 22. More in the town, at the north-end of George Street the soil showed 14, and in the botanical gardens adjacent, 15.

This Leith valley is another area with considerable market gardens cultivated largely by Chinese whose produce is distributed in the city.

The School mainly serving this area is George St., which shows a moderate goitre incidence of 20.4%.

In the right lower corner of this map is the North East Valley, a fairly closely populated area along the bottom of the valley with the ground rising steeply on both sides. The iodine figures here are all low - 12, 12, 14, 16, 16, with a 12 at Knox College, on the slope, and a 20 at the top of the hill on the same side.

The School of this district shows 16.5% goitre.

In the more central area of the city the iodine figures are more erratic, 20, 22, 16, 11 and 40 right in the centre - in a small public garden, the "Triangle".

The School nearest the Triangle, viz., Moray Place, shows 14.25%, while Albany Street School (cut by the 16 iodine circle) has 18.8% and serves a rather poor locality.

The normal School & Training College School to which pupils from various areas go has an average of 15.3%.

A study of this Map with local knowledge of the general living conditions explains a number of anomalies. It is seen that there is not necessarily an exact correspondence between low iodine content of soil and high goitre incidence. The iodine in the soil has to be taken out and passed on to the occupants of that area. That is done either by vegetables - as indicated by V. Fellenberg's work (loc.cit.89 & 90) - or by water, though the amount in water at any time is small, judging by the river samples examined. Occupants of an area relatively rich in iodine, as at part of St.Kilda do not necessarily get the iodine of their own soil. In actual fact this area is closely built with

relative ly/

relatively little space for individual vegetable gardens so that the inhabitants draw their vegetables mainly from those grown on a soil with iodine content of 15 to 36. The result is a school goitre figure of 19% (at Musselburgh School) or 18.3% (at Forbury School).

North East valley with a fairly uniform and moderately low iodine figure, has, on the whole, rather better houses and larger garden space so that the vegetables are probably either home grown or obtained from market gardens at the upper end of the Valley - not shown on map - or from similar sources in the Leith valley. Thus the soil iodine figure actually approximates to that of the vegetables consumed in St.Kilda and the goitre % is very similar - 16%.

The hill suburbs vary greatly in facilities for growing local produce and still more probably in the amount of green food eaten as the social status varies. In the Kaikorai a number of the houses are small and closely placed and a large section of the population works in the woollen mills there.

Taking the average of all the iodine estimations so far done for Dunedin, viz. 64, we find it to be 30.25 parts, and, if the three high figures seen in St.Kilda be omitted the average is 22.0% - a figure moderately low, but high compared with e.g. the prevailing figure in the Balclutha area. The school goitre percentage for all schools in Dunedin works out at an average of approximately 17 - a moderately low figure, much below the Balclutha average.

Proximity to the sea does not seem to confer any particular immunity to goitre in Dunedin, for those schools further away present a rather better average than those (as at St.Kilda)

St.Clair/

St.Clair close to the beach.

### VIII. Discussion:

In the foregoing chapters a number of observations on goitre in New Zealand have been presented. It is now desirable that these be discussed in conjunction with such information as is available on the subject from other sources, and such conclusions be come to as seem reasonable and in accordance with the facts so far available.

#### AETIOLOGY.

It is probably necessary, under this heading, to separate the causation of primary Exophthalmic goitre from the "simple non-toxic", and "Toxic", non-exophthalmic types. The exophthalmic goitre supervening on the previously - and usually old standing - simple, or even toxic, goitre need not be specially considered here as the preceding condition is the important one.

The primary exophthalmic goitre - the type of case occurring either a few days or weeks in a young patient showing no previous evidence of goitre, and histologically showing pure hyperplastic changes -- is usually assumed to be due to some abnormal nerve stimulation of the thyroid. In support of this is Cannon's well known experiment (92) of joining the anterior root of the right phrenic nerve with the right cervical sympathetic. Burget (93) repeating Cannon's work did not get such striking results, and certainly no thyroid hyperplasia. Wilson (94), on the other hand, by electric, mechanical, or bacterial stimulation to the superior cervical ganglion in goats produced the histological picture parallel to those found in the various stages/

stages of progressive and regressive exophthalmic goitre.

He concludes that his work supports the suggestion that in exophthalmic goitre the thyroid receives its stimulus to overfunction through its nerve supply, as a result usually of local infection in the cervical sympathetic ganglia.

In these primary exophthalmic cases, although it is frequently stated that there was no goitre or thyroid disturbances previous to the acute onset there have been no observations, so far as I know on the basal metabolism, iodine content of food etc., before the onset of the symptoms - naturally, as the onset is unexpected it is unlikely that such observations could be made.

If there is any common underlying and predisposing factor to all goitres, including the primary exophthalmic, it might be expected that, in endemic areas, where simple goitre is common, exophthalmic goitre should also occur relatively frequently. Grotti (loc.cit.39 (p.374)) states as follows - "Another proof in favour of the hyperfunction of the thyroid is the fact that exophthalmic goitre seldom occurs in regions where goitre is endemic, namely where the thyroid is permanently and endemically in a state of hyperfunction. Even when such endemic goitres become overactive the worst they can do is to give birth to mitigated forms of hypothyroidism, such as thyrotoxic goitre, nervousness, etc. They seldom reach the fully developed thyrotoxic clinical picture. As soon, however, as we consider regions where goitre is not endemic or mildly so, where consequently the thyroid gland has retained its full functional capacity, there Basedow's disease becomes very frequent and severe in its form."

This statement receives support from the New Zealand data above quoted. Looked at from this point of view it will be seen (Table B. *Appendix B*) from the returns of total cases in N.Z. hospitals that exophthalmic goitre bears a wonderfully constant relation to other forms of goitre. In the more detailed analysis of the three larger hospitals ( *Appendix F* ) an approximately similar proposition obtains. Auckland & Christchurch have 28.57 & 29.6% exophthalmic goitres respectively, but the toxic (non exophthalmic) cases in Auckland are 33.34% against 15.79 at Christchurch. The greatest percentage of cases in the latter city being "simple" (non-toxic). As indicated by the School goitre figures Christchurch is a definitely endemic area.

Dunedin may be regarded as coming between Auckland and Christchurch as regards amount of goitre, and here the proposition of exophthalmic cases is 39.80 against 22.34 toxic and 37.86 % others.

It will be noted also the much greater preponderance of females over males having exophthalmic goitre, corresponding therefore to the proportion in other forms.

Of course probably many of these cases so returned were cases of secondary exophthalmic goitres supervening on previous "simple" goitres. Study of the specimens of exophthalmic goitre sent to the laboratory supports this, and, incidentally, these agree with the hospital case statistics. Thus, out of the 180 specimens examined and recorded - see *Appendix J* -

22.8% were exophthalmic, 32.2% toxic (non exophthalmic), and 31.7% "simple" (non toxic).

Of this 22.8%, as far as the available information shows, only 6 out of the 41 cases were under 25 years, and of these 6 only two measured the duration of their illness in months, the remainder in years.

Thus, whatever be the immediate precipitating cause of exophthalmic goitre, and the evidence seems in favour of it being a nervous stimulation, it would appear that it is more likely to occur in a population predisposed to the simpler forms of goitre. Once started a vicious circle is begun, the thyroid being overstimulated increases the metabolic rate, which in turn accentuates the stimulation, until the overstimulated gland becomes exhausted.

A break of this vicious circle may be made by rest, to reduce the need for activity of thyroid, or by removing the over-acting tissue. The exhibition of iodine to an exophthalmic goitre is held by many to be dangerous and certainly an exacerbation of symptoms may occur but I was much interested to learn from personal conversation with Dr. W.J. Mayo during his recent visit to New Zealand (1924), that, at his clinic, patients with exophthalmic goitre before operation during the preliminary rest receive small, carefully graded doses of potassium iodide with the idea of causing involution of the gland to a more colloid state - on the basis of the work of Marine & Feiss (loc.cit.61), and Marine & Rogoff (loc.cit.62 & 63). Thus, from another aspect, exophthalmic goitre corresponds to the more simple forms.

The remaining forms of goitre can be grouped together from a general aetiological point of view. The term "endemic goitre" embraces them, and a discussion of factors concerned in this will equally apply to sporadic cases, in which however, other individual factors may be operative also.

To recapitulate all the suggested causes of goitre would be a needless waste of time and outside the scope of this thesis. Most of the general works on the subject devote considerable space to the various theories thus in Grotti's book (loc.cit.39) thirty odd pages are occupied by these. McCarrison (loc.cit.71), while also referring to various prevalent ideas regarding endemic goitre, is imbued with the toxic or infectious nature of goitre and even quotes Marine & Lenhart's work on fish (loc.cit. 1,2,3,4) in support of his contention; e.g. he suggests at p. 105 (loc.cit.71) that the iodine, or perchloride of mercury, though in infinitesimal amounts, prevented goitre by their antitoxic effects.

That he has had to modify his infectious hypothesis will be seen later.

In so far as they can be applied to conditions obtaining in N.Z. certain of the current theories must be examined.

Infection: McCarrison (loc.cit.71,p.57) quotes Rosnow as having grown a streptobacillus from a number of thyroids removed for Graves disease, while Kollé, Thompson & McCarrison himself (95) were unable to recover organisms from simple goitres as far as the thyroids themselves were concerned. McCarrison, however, describes good results from removal of contamination from waters, food etc., both in human beings - in India - and in his experimental animals, and concludes that goitre is due to absorptions of toxic bacterial products from the intestine, i.e., a positive action on the thyroid stimulating it to activity or damaging it, or both. Burget's work (loc.cit.93) in which he gave to cats faces from goiterous patients and dogs and got no

goitre/

goitre as a result does not support McCarrison's view of the faecal contamination, also Sasaki of Heidelberg (cited by Grotti) while producing thyroid enlargement in rats by faecal contamination was able to prevent such enlargement by the addition of iodine or thyroïdin, or even tyrosin.

With the idea that there might be an association between goitre and enlarged tonsils and adenoids in children, as noted by Buford, (95 a.), I asked Dr. MacCreedy to look into this during his examination of school children.

So far as his observations go, (see Appendix I), no correspondence is seen.

The question of faecal contamination of food and water can be excluded, I think with certainty, in the majority of cases as the hygienic conditions generally are very good in New Zealand.

Water: From earliest times a relation has been noticed between water and goitres, and all kinds of water have been blamed.

When the basis of this charge against water is examined in more detail it is rather difficult to find any adequate reason for it, as spring water is incriminated in one area, river water in another, snow water in still another, and so on.

But the position might still be stated with much truth in the words of Dr. Lucien M. Mayet (96), in discussing cretinism and endemic goitre particularly in the French Alps.

"On a, suivant la mode du jour ou les tendances d'esprit des auteurs, accusé l'absence d'iode dans l'eau (Chatin), la présence de micro-organismes (Grasset, de Riom; Rappin .....) etc.; tout récemment le radium a été très sérieusement incriminé. En réalité nous ne savons rien encore, sinon que les préparations

iodées/

iodées guérissent assez facilement le goitre à son début."

The first satisfactory experimental demonstration - so far as I am aware - of a direct connection between water & goitre was that by Marine & Lenhart in their work already quoted, (loc.cit.1,2,3,4).

Where they showed, in fish, that the contamination of water in fish ponds, or the overcrowding of these ponds, led to the development of fish goitre. This could be prevented by thinning the fish, or increasing the water flow, or adding iodine in minute amounts.

McCarrison (loc.cit.71), as already mentioned, blames the water, merely as a vehicle for <sup>toxic</sup> matter.

Kappenburg (97 ) reports a number of experiments on rats. He found little difference in the size of thyroids in wild rats (*mus decumanus*) whether they had lived in places with no goitre or places where it was prevalent. In Utrecht goitre is frequently seen: in Sneek (North Holland) it is never observed.

Rats in Sneek were given Utrecht water and no goitre or histological changes resulted. Similar animals kept under comparable conditions at Utrecht developed thyroids twice as large as normal and showed goitre changes histologically.

Boiling the water did not prevent the thyroid enlargement. Similar results are recorded at Haarlem by Potter (98).

At the annual meeting of the New Zealand Branch of the British Medical Association, Dr. Colquhoun (99) then Professor of Medicine at Otago University, opened a discussion on goitre and gave the results of a circular questionnaire sent by him to medical practitioners in all parts of the Dominion. He limited his

question/

questions to four, "(1) Is goitre endemic in your district or sporadic ? (2) Is there any permanent cause in your district which may lead to goitre, such as glacial water, water otherwise charged with foreign matter. Are there any other circumstances which in your opinion may be etiological ? (3) Is exophthalmic goitre common in your practice ? Can you give any personal experience which may throw light on its etiology ? (4) Can you make any suggestion as to treatment of either form ? "

The replies to these questions form instructive reading and correspond very closely with the school goitre figures recorded above. Thus the distribution of endemic goitre, based on the replies, is as follows :-

South Island - Balclutha, Otantau (Southland), Lawrence, Roxburgh (Clutha Valley), Mataura, Timaru, Ternuka, Geraldine, Ashburton, Fairlie, Rakaiia (Canterbury plain), Christchurch, Murchison.

North Island - Wellington, Lower Hutt, Hamilton, Gisborne, Whakatane, Wanganui, Onehunga, Uriwera and certain other main districts.

With regard to the water supply and also geological formations - all varieties were found. Thus in Christchurch the supply was very largely artesian and of a high degree of purity, chemically and bacteriologically; in some of the main districts of the North Island much of the water used came from hot springs. At Balclutha rain water was the main source of drinking water. At Geraldine the water supply was partly from creeks and rivers, some like the Rangitata and Orari being snow fed, and partly from wells driven deeply into the shingle.

It would take up too much space to quote much further from this paper - which was reprinted in pamphlet form - and I shall

merely/

merely refer to the report from the Doctor (Dr. Stenhouse) at

Balclutha. "In this district goitre is very common, ...

I have noted a number of mild cases (parenchymatrus) in young boys lately. Exophthalmic goitre is also common ....

As regards the water question : the Clutha is both glacier fed and practically always contains a large amount of mining and dredging debris. On the other hand, the river water is not much used for personal purposes, nearly all use rain water stored in tanks: it is my impression that rather more than half my cases of ordinary goitre come from the island (Inchclutha) and the other flats on the immediate banks of the Clutha, but a respectable number of the cases come from the country remote from the river...."

As has been noted above the Clutha river had no parts iodine in 900 million, the Taieri 1 part in 950 million and the Leith 2 parts in 900 million.

This as far as New Zealand is concerned there seems no direct relation between water supply and goitre.

Food: Chalmers Watson (100 ) studied the effect of different diets on rats and found a meat diet produced a loss of colloid and hyperplastic state in the thyroid.

Burget (loc.cit. 93 ) repeating previous work found, similarly, that a high protein diet, in rats, caused hyperplasia, also rats kept under unhygienic conditions developed hyperplasia on a standard bread & milk diet, though he states that young growing rats on a high protein diet do not develop hyperplasia.

That the question of the food, qua food, of human beings, cannot be an essential factor is seen in all the literature on endemic goitre and is also exemplified in New Zealand. Thus the

food/

food in Christchurch is the same in general character to that in Dunedin, and the general diet of one group of country people is similar to that of any other group. Speaking generally there is probably more meat consumed in New Zealand than in some other countries but this is fairly universal in New Zealand, from the fact of the cheapness of meat.

There are, as yet, no adequate statistics as to the average diet of school children in New Zealand, but these will be forthcoming. I hope in the near future as Dr. Paterson, the Director of School Hygiene, is now getting this investigation under way. One can say, however, that even among school children the diet is probably rich in protein with fewer vegetables than are desirable. One interesting fact is the high goitre incidence right along the Clutha valley, even in the fruit growing districts of central Otago where fruit is available in any quantity for children and adults.

Soil: The geological nature of the soil in relation to goitre has been studied by a number of observers.

Tolman (101 ) in an investigation of goitre in America, from the public health point of view, gives a general review of the geological relationships, thus -- after noting that no satisfactory correlation is possible between water supplies and goitre - he states, "We have, however, come to a realisation that goitre is more or less definitely associated with the geologic formation from which the drinking water is derived, the upper Palaeozoic and Lower Mesozoic areas being most affected. Goitre reaches its greatest endemicity where the course of the water is from rock

strata/

strata of the Carboniferous period, though it occurs among the more ancient Devonian and Silurian rock and the more recent Permian and Triassic. In England, goitre is practically absent in the Silurian, Devonian and Permian formations, but is endemic in the Cretaceous from which latter it is practically absent in this country. Apparently volcanic formations, the crystalline rocks of the Archaic period and all deposits laid down in fresh water are free from the goitre-producing characteristic. The region of greatest endemicity in the United States, namely, about the Great Lakes and parts of West Virginia & Virginia are Palaeozoic areas. Goitre is also slightly prevalent in parts of New Hampshire, and here again this formation occurs. We again find the Palaeozoic era represented in Edmonton, Province of Alberta, Canada, where reports would indicate the highest endemicity to be encountered in North America. It is interesting to observe at this point in West Virginia, that goitre follows the coal measures more particularly than the limestone formations with which it is commonly associated. This seems to be contrary to the experience of Clark & Pierce of the United States Public Health Service, who made a study of goitre among the school children of eleven counties of west Virginia and nine counties of Virginia."

"The association of goitre with certain geologic time would indicate that the disease is not caused by a living organism, but is due to some substance derived from marine animals in past time. The character of this substance is not known, but experiments indicate that it is not retained by a Berkefeld filter and that its goitre-producing property is destroyed by heating to 70°C. It is of course possible that goitre is a deficiency disease,

that/

that the marine animals of geologic time used up a certain substance in the water that is essential to animal economy. This theory is severely shaken, however, by the fact that heat evidently destroys, the goitre-producing element, but nevertheless it should not be entirely abandoned at the present stage of our knowledge."

In Italy, Muggia (102) refers goitre to geological and meteorological conditions and denies infection. He names endemic goitre "Mountain thyroid" and he claims that where goitre is endemic there is no such thing as a healthy thyroid.

In Spain, Gorganes (103) studied endemic goitre in the high valleys of Alberche and Tormes where he ascribes the occurrence of goitre to geological formations of the archaic group, granite, gneiss, and crystalline deposits.

In Bavaria, Weichardt & Wolff (104), on the other hand, could find no proof that geological conditions have any influence on endemic goitre.

As has already been noted in New Zealand and shown in the maps of geological formation and school goitre incidence the greatest incidence of goitre is along the line of rivers, e.g. Clutha on on plains traversed by rivers, e.g. the Canterbury plains. Such areas, generally, are more recent sedimentary deposit, river gravels, etc. Volcanic areas, such as Mount Egmont (New Plymouth) show, on the whole, less goitre. But exceptions occur in both cases, e.g. along the Waitaki, the goitre figures are much lower than along the Clutha, while at Timaru and Dunedin, although both show volcanic formations, there is more goitre than at New Plymouth or Auckland.

Iodine:

From its relation to the thyroid gland, as originally shown by Baumann (loc.cit.46) and to the thyroid hormone as recently demonstrated by Kendall (loc.cit.50-54) iodine has attracted a large amount of attention in relation to goitre.

The studies of Marine & Lenhart (loc.cit.1,2,3,4,29,36) of Wilson & Keldall (loc.cit.32), of Plumner (loc.cit.33), and many others previously referred to, all strongly suggest some close relationship between iodine and thyroid structure and goitre. But exactly how iodine is related to goitre, particularly endemic goitre, has been a subject of much dispute, some indeed such as Hirstfeld & Klinger (105) regarding goitre as of metabolic origin but not due to lack of iodine, while perhaps the majority regard the lack of iodine as an important predisposing cause of goitre. Even McCarrison has departed from his purely infectious or toxic causation of goitre and recognises the importance of iodine for he says in 1922 (106) that if animals be confined in dirty cages there may be goitre which may be prevented by clean cages. "Further if an additional supply of iodine be provided, or cod liver oil be given, even though still in dirty cages, goitre will not develop.".... "A sufficiency may become an insufficiency in presence of unhygienic conditions. "

"It is obvious, therefore, that the factors which give rise to goitre centre round the supply of Iodine and the needs of the thyroid for iodine. Now the supply of iodine is dependent on a multiplicity of factors both extrinsic and intrinsic to the body. It is dependent on the iodine supply of food & water; and this in turn is dependent on the altitude, distance from sea coast, and the iodine content of the soil from which both vegetable foods

and water derive their iodine."

The giving of cod liver oil as a preventative by McCarrison receives support from Murray's work (107) on thyroid changes in experimental rickets. He found cod-liver oil "acts on the thyroid in same way either by preventing destruction or increasing production of colloid" --- acts, in other words, as iodine acts, and, as shown by V. Fellenberg (loc.cit.90) cod-liver oil contains from 3370 to 7200  $10^6$  gm. iodine per kilo fresh substance and is thus very rich in iodine as compared with most food stuffs.

Hunter & Sutherland Simpson (108) in examining thyroids of Shetland sheep which had fed on a diet of marine algae found small compact glands very rich in iodine. Although the exact iodine content of the marine algae was not examined it is safe to assume, in view of analysis of sea growth, that it was relatively high.

E. Smith (loc.cit.5) in his study of foetal athyrosis in pigs found that the only possible difference between the feed in affected areas and unaffected areas was a slight difference in the iodine content in the former. The addition of iodine - or thyroid gland - to the feed of the sows prevented goitre in the offspring. Hart & Steenbock (109) criticise the conclusion of Smith that the foetal goitres are due to lack of iodine in the feed and claim to prevent it by varying the protein content of the same feed. They admit, however, that iodine will prevent it and conclude that the bad results are due to loss of iodine or faulty assimilation rather than a deficit in the food. If we examine the findings in New Zealand, it will be found that the one thing that most closely approximates to the goitre incidence/

incidence especially in schools is the iodine content of soils. It may be objected that there are many exceptions and anomalies as for instance in Dunedin, and certain parts of North Otago such as Oamaru, but, as has been shown, if a sufficient number of iodine estimations of any one area be made marked and abrupt differences may occur. But, unless the population is actually deriving its iodine supply, through vegetables mainly, from the area examined there is no guarantee that iodine content and goitre index will correspond. We have seen how in Dunedin the average goitre figures is higher than some areas would suggest and lower than others, but the mean corresponds to a rather low iodine figure, which is the figure for the main market gardens. At the lower Clutha area - Balclutha district - the iodine figures, so far as at present examined, are all very low and the goitre index is uniformly high: so also in North Canterbury.

If we assume each section of a population subsisting mainly on the vegetable produce of its own ground then we should expect to find the iodine figure and goitre index corresponding. This is what is seen in North Canterbury and Lower Clutha for larger sections of population <sup>but</sup> we have yet to demonstrate it on a number of small, adjacent, sections e.g. at Dunedin. However, I feel this is a reasonable explanation of the objection raised against the deficiency of iodine in the food as the cause of goitre. McCarrison (110), in reviewing the English version of the French edition of collected papers by Dr. F. de Quervain of Berne, writes as follows :- " 'Endemic goitre is a reaction of the thyroid gland, partially hyperplastic and partially neoplastic. It usually begins in intra-uterine life, and develops particularly during the second and third decade.

This reaction occurs more frequently in the female than in the male, and is probably caused by auto-intoxication from the intestine ..... The introduction of iodine into the organism in physiological quantities is capable of arresting this reaction without doing any evident harm to the general economy of the organism.' There are, as the author says, objections to the theory 'so plausible at first sight,' that a deficiency of iodine in the food is the cause of goitre. Among these objections Professor de Quervain mentions 'the striking variations in the state of the thyroid, from village to village, between one family and another, although the food conditions are identical.' He concludes that the absence or presence of iodine cannot explain these variations."

We are not told whether the iodine content of the food otherwise perhaps "identical" - is the same for these different families. V. Fellenberg's analyses (loc.cit.89 & 90) indicate that the same kind of food may actually vary greatly in iodine content.

That other factors may help cannot be denied, as shown by McCarrison's experiments with the dirty cages, that toxic factors may injure thyroid structure even as they may injure any other organ or tissue no one with pathological knowledge would dispute: the effects have already been pointed out in the pathological section of this thesis. That heredity plays a part as shown by the areas of endemic goitre and cretinism is described by many writers and illustrated in Mayet's paper already

referred/

referred to (loc.cit.96). But that the factor underlying all these influences is a primary lack of iodine supply to the thyroid is strongly suggested by the New Zealand findings as here presented.

Sex: All writers on goitre, more particularly endemic goitre, comment on the frequency of the condition in the female sex, but that it is not at all infrequent in the male sex has been brought out by the recent examinations of males on a huge scale for recruiting purposes of the war. The N.Z. statistics shows this (See Table, *Appendix C*) and, as already pointed out, show a geographical distribution corresponding roughly to the incidence of goitre in other sections of the community.

Kerr (111) in America has analysed the goitre figures for recruits there and presents some interesting results. The number of cases of enlarged thyroid by years of age was greatest at age 23, viz. 15.85%. The distribution by States is given and ranges from 39% in Washington to 8% in California. An examination into the families of those men showing enlarged thyroids showed that, in the families of 4693 such recruits, 554 or 52% sisters had thyroid enlargement, 311, or 29% mothers, 176 or 16% brothers, and 33 or 3% fathers.

Hercus & Baker (loc.cit.9) have shown in N.Z. how, in school children, before the age of puberty, ~~the conditions~~ thyroid enlargement, when present, is fairly evenly distributed between the sexes, boys showing rather more than girls; but after puberty the conditions are reversed, the incidence falls in boys and continues to rise in girls.

Levin (112) studying 1783 unselected individuals in the Great Lake District of U.S.A. found 1146 had goitres.

The water supply here was three fold, there were no unhygienic condition and each household had "a lot or two for gardening." With regard to age and sex he showed goitres commenced in the 1st year in 22 to 26% examined, and advanced in both sexes towards puberty being here 94% for females and 68% for males. He then shows the mean curve of goitre percentage in the female is maintained throughout life above 80%, while that of the male drops markedly to about 20% between 35 & 40 years, with a slight rise at 42 years and then again a drop. In the first half of life the goitres are mainly simple, later occur adenomas. He concludes by showing how the liability to develop goitre is directly proportional to the length of residence in that area.

That the female makes more calls - or rather intermittent calls of more than usual intensity - upon the thyroid is well recognised and exemplified in the slight enlargement of the gland seen normally at puberty, menstruation and pregnancy. That there is a direct relation between these normal claims of the female on the thyroid and the greater frequency of goitre in the female seems very probable. Marine (113 ) puts the relation thus : "The thyroid enlargement is in the nature of a *work hypertrophy* to stimulate metabolism, identical in appearance so far as we know, different only in degree from that seen in simple goitre. Both of these reactions can be controlled and prevented either indirectly by giving iodine or directly by giving the iodine-containing hormone in physiological doses."

While Snell, Ford, Frances & Rowntree (114) and Christie (115) have shown that, in some instances during <sup>the</sup> menstrual period the metabolic rate in girls may be increased to 15% above normal. Whether this is due to increased thyroid activity, or not, has

not, so far as I know, been shown, but it suggests an explanation of the thyroid enlargement at such times.

What the exact explanation of these intermittent enlargements may be & how they are related to the activity of the ovaries or calls of the foetus is outside the scope of this thesis to discuss.

Pathology: The basic pathological changes histological, and chemical, and functional, in goitres have been so fully and ably presented and discussed by Marine & Lenhart (loc.cit.1,2,3, 4, 28, 29, 36, 73), Marine & Feiss (loc.cit.61) Marine & Rogoff (loc.cit.56, 62, 63), L.B. Wilson (loc.cit.30,38,45,94) Wilson & Kendall (50, 51, 52, 53, 54), and Plummer (55) that they need not be here recapitulated. In the chapters on the pathological changes found in N. Z. specimens of goitre and in thyroids removed post mortem it has been shown that the changes are similar to those described by other writers.

In order to present the pathology in proper sequence and in relation to certain observations already discussed it will be necessary to refer briefly, first to the disturbed physiological cycle and then to the altered structure. The former rests on the demands for and supply of thyroid hormone.

Kendall (loc.cit.54) estimated the iodine content of various tissues in animals and found the blood contained approximately 1.5 to 2 parts per 10 million (= 15 to 20 /1000 mgm. per 100 c.c.) (or 0.0015 to 0.002 mgm).

The tissues 2.5 to 3 parts per 10 million.

The liver 3.5 to 4 " " "

Taking the iodine as an index of thyroxin he suggests that the seasonal variation in iodine of thyroids noted by Seidell & Fenger was due to a using up of thyroxin by the tissues owing to greater energy requirements to maintain body temperature.

Hudson (116 ) studying the iodine content of the blood in dogs following thyroidectomy found before thyroidectomy the average amount of iodine in blood to be 0.0079 mg. per 100 c.c. blood, (lowest was 0.0029 and highest 0.0145 mg.) After removal of thyroid the iodine in the blood was much increased e.g. in Experiment 5 the figures were :

Before removal, 100 c.c. gave 0.0075 mg.

6 days after removal " " 0.025 "

In one experiment (No.8) the figures after removal were lower but suppuration had occurred and the animal was not eating - as the author has it, "it was not replenishing its iodine."

The giving of iodine after removal further increased the iodine in blood, while the giving of thyroid after removal reduced the iodine to an approximately normal level.

Hudson concludes that the thyroid supplies some substance which profoundly influences the metabolism of iodine not only within the thyroid but elsewhere in the body.

Rogoff (117 ) got some evidence, by the tadpole method, that the blood of a dog with colloid thyroid rich in iodine - after the thyroid had been stimulated - gave evidence of thyroid hormone ; other dogs with hyperlastic glands and no detectable iodine gave negative results.

Sharpey-Schäfer (118) however, did not notice any

effect/

effect on tadpoles by feeding them with either normal blood or blood from exophthalmic patients. He did find that the latter blood produced greater augmentation of contraction of an intestinal strip than did normal blood and that such augmentation was not due to thyroxin.

Plummer (loc.cit. 55) makes the following statements, based on his own & Kendall's work. "The amount of thyroxin in the tissues (exclusive of the thyroid) of the average normal man is approximately 14 mg. Kendall, from an analysis of the iodine-content in the tissues, recently estimated the amount to be 14 mg."

"The average daily exhaustion of thyroxin in the tissues is between 0.50 and 1 mg." "A shift of 1 mg. of thyroxin in the tissues of the body is accompanied by a corresponding rise or fall of between two and three per cent in the basal metabolism."

If now we piece together the various observations the position is that, normally, the thyroid is enabled to produce its hormone (or autocoid according to Sharpey-Schäfer) in sufficient amounts for the needs of the body because it gets ample raw material, one essential, possibly the most important item, being iodine. (That the thyroid is relatively rich in tryptophane, which may be a precursor of the rest of the thyroxin molecule, has been shown by Furth & Lieben (119) but it is beyond the scope of this work to consider this. ). This is manufactured in excess and stored against future needs, hence the small colloid gland rich in iodine and hormone.

Abnormal conditions - goitres - begin when the iodine supply is deficient. As we have seen this supply comes by food mainly, and of that vegetables are an important item,

these simply pass on the salts from the soil including the iodides. Hence the general starting point of goitre is the iodine scarcity of the soil. The seasonal variation of Fenger indicates more than a mere temperature effect on the thyroid, it corresponds with the seasonal variation in plant growth and therefore in iodine content of feed. Where the iodine of soil is low such lessened plant growth means still less iodine available to the animal. At the same time the thyroxin - and therefore iodine - demands of the tissues are increased, owing to need for more heat production etc., in winter - and the thyroid being unable to turn out sufficient hormone by its available area becomes active, hyperplastic, and so overcomes the immediate difficulty. Such hyperplastic gland then undergoes involution and storage of colloid, but it is a larger colloid gland with lower iodine concentration (mg.pr.g.). Obviously there are all grades of this and many never become recognisable goitres.

While the same seasonal variation must operate in vegetable foods of man, because of his more mixed and varied diet the effect is not so definitely seasonal. In addition, in the female, is the frequently recurring sexual cycle as an additional strain on a thyroid already on the borderline as regards raw iodine.

As each recurring famine of iodine occurs either as an actual diminished supply or as an increased demand on a relatively constant low supply, the thyroid responds in the same way, always increasing its total area and bulk until finally the simple, non toxic, "parenchymatous" goitre results. If the iodine/

iodine supply is increased such a goitre in time may become toxic, "non hyperplastic", simply because of its large size; the amount of active secretion is much larger than the needs of the organism and such a gland shows an iodine content per gm. normal or but slightly below this, but a greatly increased total iodine i.e. a large supply of hormone over and above all usual needs.

Once a goitre has started, however, the picture is usually more complicated. As has been pointed out in the illustration of goitres the fully developed goitre is frequently very difficult to analyse. The delicate vessels and their intimate relation to acini and stroma render them particularly prone to rupture and so haemorrhage occurs into stroma or acini. Organisation of this follows and a scar results with more or less elimination or distortion of the part of the gland concerned. This means the remaining relatively starved acini have to make good this loss on the part of the thyroid itself and so further hyperplasia, and later involutions, follow.

If, on top of this, the thyroid is directly stimulated through its nervous supply the activity, and hyperplasia, may continue and the condition of exophthalmic goitre result with the pouring out of an abnormal hormone or one incompletely formed, and poor in iodine. This still further exhausts the intake and so a vicious circle again develops, which may result in exhaustion and disintegration of the gland and even death of the host, as shown in D.B. 1/1993 (figs. 72, 73, 74, 75).

In many goitres, particularly the clinically "toxic" goitres, "adenomata" are found. That all of these should be regarded/

regarded as real tumours is open to question. Marine & Lenhart regard them as true tumours because "while iodine will constantly induce the colloid change in ordinary hyperplasia it has no manifestly similar action in the fetal adenomata." (loc.cit.28).

And yet, as described by all who have examined them and as demonstrated in the pathological section of this work, "adenomata" may be of colloid type or the "foetal" variety may revert to colloid. Study of the specimens showing "adenomata" reveals the fact that all show more or less of a capsule composed of condensed fibrous tissue in which - if not too old - remains of atrophied acini are found while outside occur usually colloid acini. The iodine content per gram is usually low, but the total amount may be high. The duration of the goitre is usually a matter of years.

The history, the appearances and the chemical findings suggest that here again has been a thyroid working over a long period on a minimal or low iodine, with intermittent waxing and waning activity, with the secondary changes, haemorrhage etc., and finally a wearing out of many acini. The less damaged may either take up and store iodine in their colloid, usually in low concentration, or may proliferate - forming the appearances known as "adenomata", or previously undeveloped epithelial groups - the intervesicular epithelium may become active and proliferate to form the same appearance/s; the result is the same. These more active foci elaborate the thyroxin which is passed out and used up so that no time is given for storage: they are kept in more or less constant activity with the result that they in turn become exhausted,

haemorrhages/

exhausted, haemorrhages occur, and various degenerative changes - as illustrated - take place and the end result is a mass of inert, degenerated tissue. Some, however, either because they are producing more than enough thyroxin for immediate needs, or because the adjacent colloid parts are acting also, regress to the colloid state.

This process, as can be seen in many of the specimens, is at different stages and ages in different parts of the gland and so is a continuous one.

That the resulting functional disturbance - the clinically "toxic" goitre - depends on the degree and extent of change is illustrated in the post mortem series, where the same types of pathological change have been shown in lesser degree, and with less iodine content variation, but with no clinical symptoms.

That the giving of iodine does not always lead to improvement in such cases is due, probably, to the fact that much of it is simply stored in the more quiescent colloid area - already low in iodine concentration - while the proliferating "adenomatous" part pours out an undue amount of thyroxin from the increased iodine supplied, and this effect is immediate and gives rise to an increase in clinical "toxicity", while only later may ~~some~~ some degree of colloid involution occur.

While one cannot deny that some such "adenomas" may be true tumour formations, it seems to me to be more in keeping with general pathological processes elsewhere to regard the "adenoma" as one form of compensatory hypertrophy, the result of long standing activity of the thyroid followed by patchy exhaustion.

This/

This is in keeping with the compensatory hypertrophy and hyperplasia of liver tissue in subacute atrophy or cirrhosis; or with the changes in the kidney in chronic nephritis.

That infectious processes aggravate the thyroid condition is admitted - the post mortem series shows examples of damage to the gland epithelium or stroma from infections; it also shows cases where no apparent histological damage has resulted from such infections, - but such aggravation has been considerably over-rated and should be regarded in the same way as an acute infection in an individual with a well marked cirrhosis of the liver: he is carrying on up to the limit of his reserve before but fails when a comparatively mild super-added injury is applied to his patched up liver tissue.

areas has resulted from improved communication and greater movement of formerly isolated communities has been noted by Mayet (loc.cit.96). This is largely a matter of more varied diet.

In discussing goitre prophylaxis in Germany Bleyer (123) thinks that the increased number of goitre cases in Germany may perhaps be attributed to the fact that since the beginning of the War the importation of guano and artificial manures into Germany has ceased and the artificial mixtures now used are absolutely iodine free.

The iodine figures for certain manures examined at Dunedin are interesting in this connection. Reference to the end of Table (*Appendix L*) will show that "superphosphate contained 0 parts iodine per  $10^7$  while Walpole island guano has 240 parts. As sea weed is not used as manure in Otago, and most of the manures, with the exception of this guano, contain low iodine, little benefit, as far as iodine is concerned, results from manuring.

While the question of prophylaxis is the main ultimate practical aim of the study of goitre the methods found useful help to support the views put forward as to aetiology and pathology viz., that the basic disturbance is one of iodine metabolism, particularly the iodine supply, or, to put the matter otherwise, all the facts, so far as at present known, support the thesis that goitre is a deficiency disease, the deficiency being iodine.

Further, it has been shown that all goitres are "simple" and uncomplicated at their initiation but in time may take

various/

various more serious forms - "toxic", "exophthalmic", "malignant."

Therefore prevention of simple goitre promises relief from many distressing diseases whose primary origin is often not recognised.

Summary & Conclusions:

1. The prevalence of goitre in New Zealand has been shown in both adults and school children.
2. Specimens of goitres coming to the Pathology Department of the Medical School, Otago University, have been analysed and the pathological changes discussed.
3. The iodine content of thyroids, both goitre and post mortem specimens, has been estimated and compared with the pathological changes.

It has been shown that the pathological changes in thyroids in New Zealand are similar to those in other countries, especially America, where goitre is common.

4. The iodine content of soils from both North & South Islands of New Zealand has been estimated: also more detailed studies of the iodine content of soils in areas of the South Island, particularly Dunedin, have been made.
5. A comparison, aided by maps, has been made between the iodine content of soil and goitre in school children in New Zealand.
6. A relation of water to goitre has been shown, viz., that water removes iodine from soil and is thus a cause of deficiency of iodine.
7. A general discussion and correlation of the findings has been given and a scheme of the general pathology of goitre regarded as a primary deficiency of iodine disease, has been indicated.

The question of prophylaxis has been referred to only.

## XII.

REFERENCES TO LITERATURE.

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