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E N D E M I C G O I T R E

with special reference to
its occurrence
in
the Loch Tay District of Perthshire.

Thesis

for the Degree of M.D.

by

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SECTION I.
INTRODUCTION.

Definition.

Various authors in prefacing articles on the subject, have defined the condition known as goitre more or less elaborately according to their own views, and one may quote the three following definitions as typical of those which have until recently held the field:-

- I. "Goitre is a term in use for all enlargements of the thyroid gland." Murray¹.
- II. "Goitre is a hypertrophy of the thyroid occurring sporadically or endemically." Osler³.
- III. "A goiter is an enlargement of the thyroid gland not due to malignant tumour or inflammation." Da Costa⁵.

Lately, however, one has noticed the appearance of more searching definitions which would indicate the condition defined above as merely a symptom of a general disease, and as an example of these may be quoted the following, submitted by McCarrison⁶⁰ :-

- IV. "Goitre may be defined as an infectious disease in which the seat of the infection is the intestinal tract, and of which the enlargement of the thyroid gland is the dominant symptom."

A glance at numbers I, II, and III, will show that they are/

are not strictly superposable, Murray's obviously including cases excluded by Da Costa's, and resembling or differing from Osler's according to the construction put upon the word "hypertrophy". Again, as the matter is still 'sub-judice', so to speak, the adoption straight away of a definition of the type of number IV might be liable to prove irksome; wherefore it behoves us to draw up at the outset of this thesis a simpler definition, yet one which will serve as a clear working basis for the study of the condition. My experience of the disorder as it exists in Perthshire leads me to accept at the present juncture Robinson's¹⁸ statement that "A goitre is a simple, cystic, fibroid, or fibro-cystic enlargement of the thyroid gland which is benign in nature, generally increases slowly, and often continues for years", with the reservation that before a thyroid should be classed as a goitre it should be visibly enlarged. This reservation appears to me to be necessary if there is to be any satisfactory companion of the reports of various observers, although from a pathological point of view it is not strictly justified (v. below Section V).

Synonyms.

Of late years there has been manifest in this country a tendency to drop the older and etymologically misleading term "Bronchocele" (Greek - Bronchos, the windpipe, and kele, a tumour or swelling) and likewise the/

the terms "Derbyshire Neck" and "Nithsdale Neck", which tended to convey an impression of limited geographical distribution, and to substitute the non-committal French (or originally Swiss) term "goître" (Latin - guttur, the throat) or its Americanised version "goiter".

In 1817 Alibert⁸ introduced the term "Thyrophraxia" to describe the condition; some years later Conradi applied to it the title "Cynanche Thyroidea"; and still later Robinson²⁰ resurrected the old French name "Thyreoccele", which term, if it be an allowable practice to label a disease with the name of its predominant symptom, is probably the most correct of all.

The term "Tracheoccele" originally used by Heister in reference to goitre is now used to designate encysted air-containing tumours which have developed in the course of the trachea (an excessively rare condition).

The usual German equivalent to the word "goitre" is "Kropf", but in Germany too we meet with a varied nomenclature, viz:- "Struma", "Gossum", "Hernia Gutturalis", "Luftröhren-bruch" (literally - hernia of the windpipe).

In Italy the condition has been referred to as "Gozzo" and "Broncocale". For further foreign equivalents, see Appendix A.

Introductory/

Introductory Remarks.

On the subject of endemic goitre in Perthshire, my interest was aroused by the facts:-

First - that, so far as I have been able to discover, the area affected has not yet been described, and is uncharted on goitre maps.

Second.- that even in the area (although in one village about 15% of the population show the condition) the people seem to be only dimly aware of the existence of an endemic.

Third - that in the literature of the disease one is confronted by statements such as the following:-

". the disease is by no means prevalent in Scotland."9; ". . . . in Scotland bronchocele is rare. . . . "10; ". . . . some mountainous contries are almost exempt from goitre, as for example . . . in the Highlands of Scotland where it appears to be almost unknown"65; while Bircher states that goitre is uncommon in Scotland11.

(It has of course been shown that districts for many years free from the disease may become afflicted with it endemically, and that other districts where it has long been so existent may come to show a decrease in its prevalence; and this might discount the first and second of the above extracts which are from works bearing the dates 1892 and 1858 respectively, and also Bircher's statement, which was made in 1883. The third extract, however, is of so recent a date as
January/

January 1913 and cannot admit of this objection.)

Occurrence of Endemic Goitre in Perthshire.

This is gone into as fully as my information will allow under the heading "Geographical Distribution" and it will suffice here to give a short account of the climate, topography, etc., of the district referred to as "the Loch Tay Area".

Extent of area, etc.

As is described below, the region of endemicity, particularly referred to in this thesis includes the greater part of the area lying between the parallels of 56'20" and 56'40" north latitude, and between the meridians of 3'40" and 4'20" west longitude - i.e., the district which extends from the confluence of the Tay and Tummel in the East, Westwards along the valley of the Tay to Killin at the head of Loch Tay (a distance of some thirty miles) and from the Tay and Lyon confluence five miles above Aberfeldy to about halfway up Glenlyon (a distance of fifteen miles).

Physiography of Area, etc.

The surface configuration of the district outlined above is typically that of a mountainous region, viz:- a mass of elevated land rising into many lofty peaks and cut into by comparatively narrow valleys.

The main lie of the Tay valley at this point is from S.W. to N.E., Loch Tay extends ($14\frac{1}{2}$ miles) from Killin to Kenmore, flanked on both sides by high mountains/

mountains (Ben Lawers on north side - 3984 feet); from Kenmore to Ballinluig (15 miles) the hills are less lofty and less bold in outline, while the river winds for the most part in a somewhat zig-zag fashion over a narrow strip of flat haugh lands of alluvial deposit.

The Lyon flows almost due west and east along a wild and narrow glen overhung throughout its greater part by high precipitous mountains which rise almost direct from the banks of the stream.

Density and Distribution of the Population.

By far the larger part of this tract of country is uninhabited mountain and moorland, the inhabited portion being practically limited to the lower lying strips of country (between 250 and 1000 feet contours) lining the rivers. Of this latter portion all, save the nine mile strip from Aberfeldy to Ballinluig, shows a density of population of from 1 to 64 per square mile, the short strip referred to giving a return of from 64 to 128 per square mile, for which the town of Aberfeldy (1679) is mainly responsible.

Excluding the inhabitants of Aberfeldy, most of the people are land workers - farmers, crofters, agricultural labourers, etc.

Rainfall.

Situated as it is in the critical region between the wet western division of the country and the district of low rainfall in the east, the area is intersected/

intersected by iso-hyetal lines which run mainly north and south and lie on a steep gradient - the rainfall to the western extremity being from 50 to 100% greater than the eastern.

Thus the yearly average of four years (1908-9-10-11) at a station (Dunros, Strathtay) towards the eastern end was 34.44 inches, and at one (Meggernie Castle, Glenlyon) towards the western, 60.32, my own gauge at Aberfeldy giving, for the same period, an average of 35.54 inches per annum¹².

The rainfall is fairly evenly distributed over the year and, as the figures testify, is nowhere in the area excessive.

Temperature.

The mean shade temperature (as calculated from daily readings, over several years, of standard maximum and minimum 4 foot thermometers) at Aberfeldy I find to be about 47°F. for the whole year. Extremes are not common - January, the coldest month, averaging 35.4°F. and July and August about 59°F.

Geology of the Area.

In view of the fact that certain geological formations were at one time held to have a very definite causal relationship to the occurrence of endemic goitre, and more particularly because modern research points to a more than accidental association, it is well that the subject should have thorough ventilation. I therefore append/

append a brief sketch of the rock formation of the area under consideration.*

The superficial deposits (J)[†] are mostly of glacial origin, viz:- boulder, clay, moraine stuff, and fluvio-glacial gravels. In addition, there is a minor accumulation of stream alluvium (K)[†] along the course of the rivers and burns, at the deltas where they debouch into the loch. With the exception of one or two masses of intrusive felsite which is igneous in origin the whole of this area is highly metamorphic (v. Maps V and VI).

On the South side of the Tay valley from Killin to Ballinluig, the main bulk of the rock is mica schist (A) with, between Ardtalnaig and Ardratnaig, a considerable hill mass of intrusive felsite (H), and, between Ardtalnaig and Kenmore, numerous outcrops of thin sills of sheared epidiorite (B). The Loch Tay Limestone formation (C), which plays an important part in the disposition of the rocks on the north side of the Loch, at one time overlay the mica schist on the south side but, with the exception of a small cap on Meall-ne-Craig overlooking Ardeonaig, is now entirely denuded.

To the north a greater variety is seen in the dividing range of hills between Loch Tay and the eastern half of the River Lyon (Shown best possibly in Section/

* Abstracted from "Notes on the Geology of the Tay Basin" by B.N.Peach, LL.D., F.R.S., and J.Horne, LL.D., F.R.S., in Scottish Geographical Mag. Jan.1904. p.31., and from written notes kindly furnished to me direct by Dr Peach.

† Letters are references to Geological Maps No.V and VI.

Section - Map VI). Overlying the mica schist (A) which outcrops only slightly towards Loch Tay, though more extensively towards Glenlyon is the Loch Tay Limestone (C) which outcrops along most of the western two-thirds of the loch; overlying this is a layer of garnetiferous mica schist (A¹), and over this again, separated from it by a thin sill of sheared epidiorite (B¹), lie the phyllites (D) which are found on the summits of most of the hills here and westwards beyond Killin. Here and there overlying the phyllites on the northern aspect of the range are small residual islands of a Black schist (E) formation, over which are found occasional masses of quartzite (F).

The remainder of the area, i.e. the range of hills to the north of the Lyon valley (eastern half), and forming the northern wall of the Tay valley from the Tay - Lyon confluence eastwards to Ballinluig, is divided distinctly by the great Loch Tay fault which runs north and slightly east from Fearnan (four miles west of Kenmore) on Loch Tay in the direction of the west end of Loch Tummel. That part of the hill range which lies to the east of this fault was at one time continuous with and reproduces the structure of the land to the north of Loch Tay. To the west of the fault the outcrops are almost entirely of quartzite (F) and quartzose flagstones (C)

Chemical composition of these rocks - with especial/

ial reference to the presence of lime and magnesia *
etc.

Loch Tay limestone on analysis shows 53.33% of Carbonate of Lime and 7.87% of Carbonate of Magnesia⁺, etc.

Phyllites are highly calcareous and contain both lime and magnesia. Epidiorite sills contain usually a good deal of the carbonates of lime and magnesia.

Black schist contains much pyrites (Iron Sulphide). The superficial deposits counting as they do for the most part of comparatively unweathered debris of the rocks over which the ice has passed⁺ must contain much of the carbonates, which must be leached out by the water passing over or through them.

The intrusive felsites - the feldspars of which are silicates of the alkalis - would not give rise to calcareous water.

† For report on analysis of Loch Tay Limestone v. appendix D.

* These minerals have most commonly been supposed to have a causal relationship to Endemic Goitre (v below Etiology) ≠ v. appendix F.

SECTION II.Historical Outline.

From very early historical times the condition now known as goitre has been remarked and written upon.

As far back as the time of Hippocrates (born c̄ 460 B.C.) and Aristotle (384 - 322 B.C.) it was described under the name of "Broncocele" and it is interesting to find that even at this early period its presence was attributed to the drinking of snow waters.

Leaving Greece and coming to Rome we see mention of the condition in the writings of Vitruvius who lived in the reign of Augustus, and again later in the works of Pliny the Elder (13) who referred to its occurrence in the Alpine valleys. Other Roman writers who recorded observations upon the subject were Galen (130 - 200 A.D.), Ulpian (died 228 A.D), and Celsus (14) who attributed it to coldness of the water and spoke of the use of caustic applications for its removal.

In the records of the Middle Ages we see it referred to by Albucasis, an Arabian physician, who in the eleventh century described it at some length, and again in the writings of Marco Polo, an Italian traveller, who spent the years 1275 - 1292 in Central Asia and noted its presence amongst the people there.

Later, a Swiss physician - Paracelsus - who settled in Salzburg, Austria, in 1541, described the endemic form/

form of the disease as it existed then, in and around that town, and ascribed its occurrence to the presence of mineral impurities (particularly Sulphide of iron) in the drinking water. Shakespeare again some years later obviously had in his mind the condition of goitre or bronchocele, when in "The Tempest" (15) he puts in the mouth of Gonzalo the words:-

"Who would believe that there were mountaineers
"Dewlapped like bulls, whose throats had hanging at them
"Wallets of flesh?"

As we approach more modern times, literature upon the subject becomes more abundant. Prosser in 1769 published a work entitled "An Account and Method of Cure of Bronchocele or 'Derbyshire Neck'," but the first scientific treatise on goitre appears to be that of Malacarne (16) of Turin (1789).

Mungo Park in his "Travels in the Interior Districts of Africa" (1799) noted its occurrence amongst the natives in the regions of the upper reaches of the Niger. In 1800, Fodéré - who was himself goitrous - issued his "Traité sur le goitre et sur le Crétinisme" (Paris). Other eighteenth century writers included Rush, Meckel, His, Hauslentner, Bailley, Larrey, Flajani, etc.

During the nineteenth century many monographs appeared on the subject, the principal investigators and writers being, in the earlier part, Coindet (who was the first to use iodine as a remedial measure), Roos, Schiff, StLager (who revived the Iron Sulphide theory of

of Paracelsus), McNamara (who sought to establish a relationship as regards causation between goitre and malaria), Majendie, Hedenus, etc., - and later, Baillarger (1873), Langendorff, Hurthle, Horsley, Lebert, Lebour, Virchow, Hirsch, Maffei, Kocher, H. Bircher, Wölfler, and many others. St. Lager (1867) in his "Études sur les causes du goître et du Crétinisme" gives a very full bibliography of the subject prior to his time, and McCarrison in his "Etiology of Endemic Goitre" (1913) brings the list up to date.

At different times commissions have been instituted to investigate the etiology of Endemic Goitre and Cretinism. These commissions have issued reports on their investigations and much valuable information is given. Among living investigators may be mentioned E. Bircher, Kocher, McCarrison, Murray, and Simon.

In addition to this sketch of the history of goitre there is much that is relevant as of historical interest, particularly in respect of Theories of Causation, Treatment, etc. This will be briefly touched upon in the several sections.

SECTION III.Distribution.

Goitre has a world wide distribution and few countries appear to be wholly exempt from it (v Map I - "Goitre Map of the World") though in all those countries in which it occurs it is generally confined to definite areas where it is endemic.

In treating this part of the subject I shall briefly refer to, and consider the various centres of the disease in the world, first from the purely geographical aspect, second from the physiographical, and third from the geological.

Geographical Distribution.

(For a very full enumeration of the goitre areas of the World v. St. Lager "Etudes sur les causes du Goitre et du Cretinisme" pp. 265 - 437).

Examining then the continent of Europe we find that the place of maximum frequency is in the region of the Central Alps, the disease radiating from there in various directions. Thus it occurs in Switzerland, particularly in the Valais; in Austria - in Tyrol, Styria, Upper Austria, and Lower Austria; in Germany - in Alsace, Baden, and Bavaria; in France - in the provinces of Dauphiné, Savoy, and Marne; in Italy - in Piedmont, Lombardy, and Venetia.

In France it occurs also in the province of Auvergne, and/

and between France and Spain among the Pyrenees. Otherwise in Europe it has been noted in certain parts of Russia - in the Ural Mountains and the Caucasus; in Hungary - among the Carpathians; in European Turkey (25); in Finland; and in Great Britain (v. below).

North Germany and the Netherlands appear to be wholly exempt from it and in Scandinavia, particularly in Sweden, it is rare.

The distribution in Asia offers a considerable analogy to the distribution in Europe, if the Central Asian Plateau be substituted for the Alps. From this centre of prevalence, the disease radiates in various directions and occurs along the southern aspects of the Himalayas in Bengal, Oudh, and the Punjab, (McNamara), also in Kashmir and the North West Frontier Province at the base of the Hindu Kush Mountains (McCarrison). In Asiatic Russia we find it among the Altai Mountains and in the plains of the rivers Obi and Lena; in the Chino-Tibetan frontier regions it occurs amongst the mountains at the source of the Yang-tse-Kiang (26), and it is also found in the Northern Province of China.

Elsewhere in Asia it is found on the coast of Ceylon; in Sumatra, Java, and Borneo; in the Philippines - in Macabebe near Manila Bay (28), etc.

Its presence has been noted in Africa in certain oases of the Sahara (St.Lager); near the source of the Niger (Mungo Park); among the mountains to the west of Lake/

Lake Tanganyika (29); in the Lopere and Kebuiré districts in Central Africa (30); on the coast of Algeria; in Madagascar; and in the Azores.

It occurs in South America in certain parts of Brazil and among the Cordilleras; also in the upper and lower course of the Magdalena River in Colombia and in the elevated plateau of Bogota. In fact it occurs in most of the South American countries, even as far south as Patagonia.

In North America it is found in Michigan, about the eastern end of Lake Ontario (Dock); in the Hudson Bay Territory; at Edmonton, and along the course of the Saskatchewan river (Richardson); also in the neighbourhood of the Blue Ridge in Virginia, in Pennsylvania, New York, New Hampshire, and Vermont; while Franklin observed its presence amongst the Esquimaux of the Polar seas.

Geographical Distribution in Great Britain:-

Under the heading "Geological Distribution" (v. below) a combined table of the Geographical and Geological Distribution of endemic goitre in England is given. The significance of the relationship of these two distributions is discussed under the heading "Etiology" (v. Section IV.B.)

Geographical Distribution in Scotland (v. Map. II):-

In Scotland the goitrous districts as compared with the great endemic foci of Central Asia and Central Europe/

Europe are insignificant both as regards extent of area and intensity of the disease, and the literature thereon is more than correspondingly scanty.

In 1862, Mitchell (31) described the condition as endemic in "the greater part of Roxburgh, the upper parts of Selkirk and Peebles, the eastern parts of Ayrshire (where it touches Lanark and Dumfries), the upper district of Lanark, the whole of Kirkcudbright and Dumfries, the west of Berwick, and the eastern parishes of Wigtown" and stated that it reached its greatest intensity in the upper valley of the Nith.

Kay referred particularly to its occurrence in the town of Sanquhar (a)* in Nithsdale, and Chalmers to its presence in Thornhill. (b)* where it "affects half the women", while McLeod made special mention of Wanlockhead (c) and Langholm (d) in Dumfries-shire, Hawick (e) in Roxburgh, and New Galloway (f) in Kirkcudbright

St Lager (71) in 1867 stated that endemic goitre and cretinism occurred in Perthshire, on the east coast of Fife (g), and on the coasts of Arran (particularly towards Shiskin (h) on the west), but gave no references.

McKenzie (32) in 1894 described a previously unrecorded centre in the valleys of the Clyde and its tributaries in the middle and upper wards of Lanarkshire, with points of maximum intensity in the coal-mining localities of Larkhall (i), Dalsert (j), Stonehouse (k), Wishaw (l), Carluke (m), and the agricultural districts of/

* (a), (b), (c) etc. refer to corresponding letters on Map II. q.v.

of Strathaven (n), Lesmahagow (o), Blackwood (p).

The late Professor Laycock of Edinburgh University in his lectures on the Practice of Physic was wont to mention as one of the endemic centres of goitre in Scotland the district of Aberuthven (q) in Perthshire and this, no doubt, is the part of the county referred to by St.Lager. From McCarrison's statement (already quoted*) (65) the existence of the endemic area of Lochtayside (r) would seem hitherto to have escaped notice, or at all events to have remained undescribed:

The extent, physiography, etc., of this area have already been described (v. pp.5 and 6); the distribution of the disease within it is somewhat as follows:- Westwards from Grantully (v.Map IV) to Acharn (a village on the south side of Loch Tay, two miles west of Kenmore) cases are rare, and are scattered singly and irregularly, (I know of only six or eight in this strip of country; several of these occur in Aberfeldy but are mainly imported from the outside district). In Acharn (population 90 - 100) about 15% of the people are affected; this village exhibits the greatest concentration of cases observed anywhere in the area. Westwards from Acharn to Ardtalnaig the hillface is occupied by small farms, cottages, etc., numbering in all not more than a dozen. To these houses I have traced fifteen cases, of which fifteen, ten are accounted for by three houses. For notes of cases west of Ardtalnaig I am indebted to Dr Wilson of Killin; the cases in his district/

* "Some mountainous countries ----- are almost exempt ---- as for example"----the Highlands where it appears to be almost unknown."

district are scattered singly for the most part, the distribution being indicated in Map IV (q.v.)

On the north bank of the Tay from Ballinluig to Killin, cases are very rare (I have notes of three in my own district, which extends westwards to Lawers, and of three between Lawers and Killin).

In the valley of the Lyon a small clump of cases - about half a dozen - occur in and near Fortingall. In the glen proper I have observed about the same number scattered here and there over some fourteen miles, among about twenty families.

By Medical men practising in various parts of the country I am informed that (with the exceptions of the Pitlochry and Stanley districts where the condition seems to be rather commoner) though cases of endemic goitre are occasionally met with, they are to be considered somewhat rare. My own experience however leads me to suspect that the disease may be more widespread than my information shows, for there is no doubt that unless particularly sought for, a large number of slight cases escape notice altogether; and in addition a more even distribution throughout a great part of the country is hinted at by the following data kindly supplied me by Colonel Moffet, R.A.M.C., Medical Inspector of School Children for Perthshire:-

Cases/

Cases of Endemic Goitre in School Children.*

(for years 1910-11, 1911-12, and 1912-13).

Highland District	_____	14	cases	in	8	schools
Western	" _____	2	"	"	2	"
Eastern	" _____	6	"	"	6	"
Central	" _____	8	"	"	6	"
Perth District (excluding Perth City)	_____	8	"	"	8	"

In the Loch Tay area, cases are rare in children of school age, and of the 14 occurring in the Highland District only 6 are accounted for by this area. Thus, if the proportion of affected children to affected adults is approximately constant throughout the country, it is obvious that the disease must be more prevalent than is supposed.

Physiographical Distribution:-

Although goitre is endemic in certain cities e.g. Geneva, Rheims, Vienna, etc., a critical survey of the Geographical Distribution reveals a much greater prevalence of the disorder in rural than in urban districts, and also demonstrates a distinct association between it and mountainous regions. This latter fact has long been recognised and it has even been advanced that the condition is essentially a disease of such regions. In this connection Thursfield (27) has gone the length of suggesting that reduced atmospheric pressure may bear some/

* v. Appendix E.

some causal relationship, but the etiological value of this feature of the disease and of Thursfield's explanation of it are reduced by the facts:-

1. that goitre occurs widely in the plains of India and elsewhere, as in Italy (Piedmont, Lombardy, Venetia), in Siberia (the plains of the rivers Lena and Obi), in Canada (Hudson Bay Territory), etc., etc.
2. that even among the mountains it is commoner in low lying, moist, and comparatively sunless valleys than in higher and drier situations; this has been shown by Larrey (112), Fodéré (37), Postiglione (113), Johnson (38), and others, as respects various districts in Switzerland, Tyrol, North Italy, etc., and by Gibson (39) and Humboldt (79) for the United States of America and South America.
3. that some mountainous districts are almost exempt from it - as Scandinavia.

As regards Elevation, it may occur at all heights above sea-level; thus, McCarrison (65) has seen it in Kashmir at an altitude of 10,000 feet, and, as stated above, it is present in certain localities on the sea-coast as in Ceylon, Luzón, and Algeria.

As regards Latitude, it is commonest in temperate and sub-tropical countries, though it is not confined to them. That neither great heat nor great cold can exclude its occurrence is shown by its presence in such tropical regions as Brazil, The Sahara, Java, Sumatra, the plains of India, etc., and such cold regions as the/

the shores of the Polar Seas.

Thus it is apparent that, while the condition is commonest in the deep valleys of the mountainous regions of the temperate zone, it may occur in all countries whatever may be their surface configuration or climate.

Geological Distribution:-

Much work has been done by many investigators in the endeavour to prove the existence of a relationship between the presence of endemic goitre and certain geological formations, but as the more important of the theories bearing upon this point come up for consideration under the heading "Etiology" I shall reserve the discussion of this subject for that section and meanwhile content myself with the mere setting down of several of the tables compiled from the results of these researches:-

St Lager (70) collected a vast amount of information upon this subject and the following tabulated summary of his findings as regards France has been prepared by Lebour:-

"The Goitriferous and Non Goitriferous Rocks of France".

	<u>Goitre is endemic on</u>	<u>Goitre is not endemic on</u>
Recent	_____	Alluvial deposits
Glacial	_____	Drift deposits
Pliocene	_____	Pliocene deposits
		generally.

	<u>Goitre is endemic on</u>	<u>Goitre is not endemic on</u>
	(The Fahluns of Touraine, Gironde, etc.
	(
	(The Beauca Limestone.
	(
	(The Lacustrine	
	(Limestone	_____
	(
	(The pyritiferous	
	(and Gypseous	
	(Mottled Clays	_____
Miocene	(
	(The Metalliferous	
	(Arkose of Auvergne	
	(
	(Molasse with pyritous	
	(lignites of Savoy	
	(and Dauphiné	_____
	(
	(The Fontainbleu Sandstone
	(
	(The Upper Nagelfluh
	(
	(The Gypseous Marls of Paris
	(
	(The "Calcare Grossière" of the Paris Basin
	(
	(The Brie Limestone
	(
Eocene	(Sands and Clays with pyritous	
	(lignites of the Paris Basin	_____
	(
	(Nummulitic pyritous limestones	
	(and Black Shale of the South	
	(of France	_____
	(
	(Clays with pyritous lignites	
	(of Provence and Languedoc	_____
	(
	(The chalk with flints and	The white hippurite
	(Iron pyrites of North	limestones of the
	(France.	South.
	(
	(Chalk marl	The "Urgonian".
	(
Cretaceous	(Upper greensand with iron	
	(pyrites	_____
	(
	(The gault with pyritous clays	_____
	(
	(Pyritous marls of lower	
	(greensand.	

Goitre is endemic on Goitre is not endemic on

	(_____	The Portlandian	_____
	(The Kimmeridgian (rarely)		_____
	(with pyrites		_____
		_____	The Corallian	
Jurassic	(The lower Oxfordian		_____
	(with pyrites (Kell-		
	(ovian)		_____
	(The inferior Oolite		
	((only at outcrops of		
	(well-known bed of		
	(pyritous ironstone) The Inferior oolite.		
	(Liassic, bituminous,		
	(and pyritous marls,		
	(lignites, arkoses,		
	(and shales		_____
Triassic	(The mottled pyritous		_____
	(marls of the Keuper		_____
	(The Muschel Kalk		
	((very variable in		
	(distribution)		_____
	(The Variegated grit		
	((grés bigarré)		_____
Permian	(The Autun Shales		
	((Pyritous and Bit-		
	(uminous)		_____
Carboniferous	(Coal measures (only		
	(at outcrop of pyrit-		
	(ous coals)	Coal measures	
	(Anthracite pyritous		
	(shales		_____
	(Metamorphic coal meas-		
	(ures with veins, etc.		_____
	(Carboniferous limestone		_____
Devonian		_____		
Silurian and	(Schists and other high-		
Cambrian)	ly altered deposits		
)	where they contain met-		
	(alliferous veins		_____
Eruptive		_____	Granite and gneiss	
		_____	porphyrites and other	
			igneous rocks.	
The/				

The following table has been prepared by Robinson (19) from data supplied by Lebour's paper "On the Geographical Distribution of Endemic Goitre in England" (pp. 4 - 7):-

<u>Geological Formation:</u>	<u>Geographical Distribution:</u>	<u>Goitre:</u>
<u>Post Tertiary.</u> (Deposits of sand, gravel and clay, Drift deposits)	-----	absent.
<u>Tertiary.</u> (Pliocene, Miocene and Eocene.)	(Including the London Basin and that of Hampshire and the Isle of Wight)	absent
(Chalk with flints.)	(In Surrey, Sussex (as Newhaven) Hampshire, Dorsetshire (doubtful) Buckinghamshire (as about in Beaconsfield), Kent)	present in scattered cases (rare)
(Drift chalk.)	In Norfolk	
<u>Cretaceous.</u> (Upper Green sand.)	In Sussex and Kent.	
(Gault (Folkestone Marl))		Endemic
(Lower Greensand)	Ampt Hill in Bedford. Sparingly in Surrey.	
(Wealden (Weald clay and Folkestone ferruginous sand).)	(About Tunbridge Wells, at Speldhurst, Haslemere, and Horsham)	
(Oolites)	Except near Helmsley in Yorkshire	Absent
<u>Jurassic</u>	(which extends from Teesmouth to Lyme Regis in Dorset and contains much iron pyrites except at South Petherton and near Helmsley.)	Very rare..
(Lias)		

<u>Geological Formation:</u>	<u>Geographical Distribution:</u>	<u>Goitre:</u>
	(Rhoetic Beds -----)	Absent
<u>Triassic.</u>	(M. Cheshire and West side)	} Absent.
	(of Eden in Cumberland)	
	(New Red)	} Endemic.
	(Sandstone) (In Devon, and at Wombourne near Wolverhampton.)	
<u>Permian.</u>	(Dolomitic or Magnesian Limestone)	(Practically absent.)
	(Red Sandstone -----)	
	(True coal measures)) absent.
	(Millstone grit.)	
<u>Carboniferous.</u>	(Carboniferous) grits, shales -as in Wear-dale, etc.	Present.
	(Limestone) Limestone (Along each side)	} Highly endemic.
	strata. (of Pennine Range)	
	In Malvern District, Forest of Dean, Flint,)	
	Bristol.)	
<u>Devonian</u>	or Old Red Sandstone -----	Absent or
<u>Silurian</u>	-----	(Absent or
<u>Cambrian</u>	and <u>Precambrian</u> -----	(nearly so.
<u>Eruptive</u>	- Granite, porphyries, etc., -----	

McClelland (40) has condensed the results of a vast amount of research into the following neat little table:-

Water derived from	% of population Goitrous.	% of population Cretins.
Granite and Gneiss	0.20%	0
Mica, Slate, and Hornblende	0.00	0
Clay Slate	0.54%	0
Green Sandstone	0.00	0
Limestone Rocks	33.00%	3.1%

The results of Bircher's investigations in Switzerland may be summarised thus:-

A.	B.						
<u>Goitre Occurs on</u>	<u>Goitre is Absent on</u>						
Marine deposits only, and especially those of the <table border="0" style="margin-left: 20px;"> <tr> <td style="vertical-align: middle;"> Palaeozoic Triassic and Tertiary </td> <td style="font-size: 3em; vertical-align: middle;">}</td> <td style="vertical-align: middle;">Periods</td> </tr> </table>	Palaeozoic Triassic and Tertiary	}	Periods	Crystalline rocks of Archiac Groups. Marine deposits of <table border="0" style="margin-left: 20px;"> <tr> <td style="vertical-align: middle;"> Jurassic Cretaceous and Post-Tertiary </td> <td style="font-size: 3em; vertical-align: middle;">}</td> <td style="vertical-align: middle;">Periods.</td> </tr> </table> All fresh water deposits.	Jurassic Cretaceous and Post-Tertiary	}	Periods.
Palaeozoic Triassic and Tertiary	}	Periods					
Jurassic Cretaceous and Post-Tertiary	}	Periods.					

He explains that where goitre occurs on the outcrop of any rocks of group B there is a basis of rocks of group A, down to which the sources of the springs extend.

As a result of enquiries directed to other countries he supplements the above by the following statement:-

Goitre occurs especially on Rocks of	<table border="0"> <tr><td>(Silurian</td><td>)</td></tr> <tr><td>(Devonian</td><td>)</td></tr> <tr><td>(Carboniferous)</td><td>)</td></tr> <tr><td>(Permian</td><td>)</td></tr> </table>	(Silurian)	(Devonian)	(Carboniferous))	(Permian)	Systems.
(Silurian)									
(Devonian)									
(Carboniferous))									
(Permian)									

McCarrison (66) described a high degree of prevalence of goitre in the eighty miles of country lying between Gilgit and Astore in Kashmir, where the land is made up of "an igneous complex composed of several varieties of granite" (MacMahon), while in Bega (New South Wales) there exists a small endemic centre over a granite formation (66)

The Geology of the Loch Tay endemic area has already been described (v. pp.7 - 8.)

SECTION IV. A.Etiology.Influence of Certain Factors.

Before proceeding to discuss the question of etiology proper of endemic goitre I shall shortly examine the influence upon its occurrence of the several factors:-

Position in the animal Kingdom

Race

Heredity

Age

Sex

Occupation

Social State.

Position in the animal Kingdom:

Investigations under this heading show that the condition is not confined to man.

In several endemic centres the thyroid has been found enlarged in dogs, as in Basle (Wilms); in rats, as in the Carinthian Alps (Von Wagner); while St.Lager(72) gives references of various writers to its occurrence in horses, pigs, sheep, goats, mules, antelopes, cattle, chamois, cats, and hyenas.

Experimentally the condition has been produced in dogs, rats, horses, fish, and also in man, but as this subject comes up for discussion in another section it may be left for the present.

Race:/

Race:-

A glance at the geographical distribution is sufficient to prove that race has no demonstrable bearing upon the occurrence of endemic goitre; no race of men is exempt.

Heredity:-

Goitre itself has never been definitely proved to be transmissible from parent to child in the same sense as syphilis has been, and the fact that children have been born with the condition already developed probably means no more than that the foetus in utero has been exposed to the same causes as the mother, and has consequently become goitrous.

It does not seem unjust however to assume that some families or members of families may be born with a hereditary tendency to the affection similar to that observed in relation to certain other diseases, notably tubercular disease, and that, should such persons be exposed to the action of the cause of the condition they will be more prone to develop it than other persons not so predisposed; or, if a different expression of this view be preferred, may there not in these individuals be a hereditary weakness of the thyroid mechanism whereby, on increased call arising for the secretion, the gland to meet the call must hypertrophy?

Various facts have been adduced in support of this idea:-

Frequently in endemic centres it is observed that members/

members of certain families are attacked, while members of other families living beside them and under the same conditions escape. I have seen a case* in point in which out of three sisters, two were goitrous; they all married and bore families:-

Sister A - goitrous - after her marriage removed to Glasgow and has had four children - none goitrous.

Sister B - goitrous - remained in the affected district (the village of Acharn, Lochtayside) and has had seven children - five, two female and three male, goitrous.

Sister C - non goitrous - living in a cottage a quarter of a mile from Acharn and using a separate water supply, has had fourteen children; two died in infancy and of the remaining twelve, four - two female and two male - developed goitre.

Of course it may be held that those living in a house where the disease occurs are most liable to infection, but this does not entirely meet the present case, as the children of sister C were at no time exposed to a common source of infection with those of sister B. It is probably necessary however to assume a certain degree of individual idiosyncrasy to explain why some members of a family should be attacked by the disease - or rather should show the thyroid enlargement - while others who are exposed to the same influences/

* See also Case II. Recorded Cases. Section X.

influences escape.

Bauer (41) has stated that persons of a lymphatic or of a neuropathic constitution are especially liable to develop goitre and this may have a bearing on the apparent hereditary character of a number of such instances, though it is of course open to question whether the neuropathic tendency is really the cause and not an effect of the thyroid condition.

Again from another aspect, Inglis(42) mentions a case in which some French prisoners, presumably from a goitric district of France, had been sent to a part of the country where goitre was not known. Some of these men formed liaisons with healthy women there, and their female offspring were said to have been goitric. Conversely however marriages which bring healthy women into goitric districts, do not seem to lessen the liability to the affection (69). Likewise cases (20) have been observed:-

- a. in which goitric children have been born of healthy parents
- b. in which cretinous children have been born of healthy parents
- c. in which women who have previously borne healthy children have, after coming to reside in a goitric district, given birth to cretins.

Revising the evidence I think one is justified in concluding that hereditary tendency has a definite influence/

fluence in the production of a proportion of cases, though it is entirely subordinate to the stronger and further reaching endemic influence.

Age:-

Goitre does not attack individuals at all ages indiscriminately.

I. Incidence in childhood:

A. In a number of cases, children otherwise healthy have been born with the condition already developed; such cases have been recorded by Fallopio (Venice 1563), Piraeus (Paris 1612), Jordan (Gottingen 1794), Bach (1885), Betz (London Journal of Medicine 1850), Robinson (1885) (20), Mooney (1911)(44), etc., while McLannahan(43) reports from Stonehouse, Gloucester, a case in which a goitrous woman who had one sister and two brothers goitrous, was delivered of a goitrous child, in which the neck measured $10\frac{7}{8}$ " at its greatest circumference.

This however is not common even in regions of high endemicity though, according to Fodéré(37), many cretins are born with small goitres the size of a walnut.

B. The question of its incidence in children born absolutely healthy is one on which authorities are not wholly agreed, probably because different observers may hold different views as to how much in the nature of a thyroid enlargement really constitutes a goitre, and because the percentage of children attacked in different districts varies according to the intensity of/
of/

of the endemic; thus, in Kashmir where the endemicity is high, McCarrison(63) states that children are as liable to be affected as are adults, as many as 65% of all the children in certain villages showing the condition.

In all cases however, it appears that the younger the child, the less is his or her liability to become goitrous(21)(65); thus according to Robinson it is rare before the age of eight. The report of the Medical Inspector of School Children for Perthshire(excluding Perth City) seems to bear this out, for in 38 cases observed in three years (1910-11, 1911-12, 1912-13) only 7 occurred in children under twelve, and of these 7 only 2 were in children under ten; of these, one was in a mentally deficient girl aet.9-10 whose physical development was equal to that of a girl of fourteen, the other was in a girl of 6-7. Nineteen cases were in girls between the ages of thirteen and fourteen.

2. Incidence at Puberty:-

As a rule in both sexes, goitre is most liable to come on at the time of puberty. This point, which is borne out by the above figures, seems to be generally remarked and to be beyond dispute; its significance is discussed below (v. Sex).

3. Incidence in Adults:-

The tendency for goitre to develop in the adult male grows less as age increases; in the adult female the/

the tendency remains raised during the childbearing period, with exacerbations of liability at certain times (v. Sex). After the menopause in women, and in late life in men, the tendency lessens though the condition may still develop, even in persons who have lived goitreless in an affected district for many years; thus Robinson(22) records a case of his own, in which a female who had resided in an endemic centre all her days, suddenly became goitrous at the age of fifty-two.

Sex:-

As a generally observed rule, females are oftener affected with goitre than are males. (Of the 38 cases reported by the Medical Inspector of School Children for Perthshire 36 were in females).

Various theories have been advanced to explain this, some rather fantastic, of which the following may be taken as examples:-

1. Women are greater water drinkers than men - a theory said to be supported by the fact that in India, where the sexes are presumed to consume fairly equal quantities of water, the proportion of men to women attacked is almost 1 to 1. (The relationship of endemic goitre to drinking water is discussed below).
2. Thursfield(27) has suggested that the carrying of weights upon the head has a predisposing effect to the disease, and that this may account for its greater prevalence in the female sex.

A study of the age distribution, etc., of goitre in the two sexes however gives us a more likely clue to the solution of the problem.

In addition to statements already made under the heading "Age" it is to be noted here:-

1. That up to the time of puberty males and females are equally liable to be affected with goitre (62).
Baillarger (45) has stated that this equality of liability continues up to the age of twenty-five, but this is probably too high.
2. That goitre in the female tends oftenest to develop at the time of the onset of the menses and may even cause delay in the appearance of this function of the female generative organs (10).
3. That during the childbearing period the goitre, if present, tends to increase, particularly during the years when the sexual organs are coming to maturity when it is often associated with anemia, with later and more definite exacerbations, sometimes during pregnancy and sometimes during lactation, and in some cases also at the menstrual periods (46).
4. That the presence of goitre in the female is frequently associated with profuse leucorrhoea (46) and irregularities of menstrual discharge, or disorder of the uterine functions; the suppression of the menses on the other hand sometimes causes or predisposes to the appearance and rapid development of goitre/

goitre (10).

5. That at the time of the menopause most women, whether goitrous or not, present symptoms closely resembling hyperthyroidism, and
6. That after the menopause the tendency to develop goitre diminishes, though women who are already goitrous sometimes show increased enlargement of the gland at this time (48).

All this points strongly to an association of function between the female generative organs and the thyroid, and that such association may be proved experimentally has been shown by Bell (124). The exact significance of this interdependence between the thyroid and the female generative organs is not yet perfectly understood, but that such interdependence exists was known even to the ancients - thus Claudius in his "Epithalamium" says:-

"Non illam nutrix oriente revisens

"Histerno poterit collum **circumdare** filo

or, according to the liberal rendering of Professor Strong:-

"Never again her nurse at break of day

"Performing service at her mistress' beck

"Shall twine the yestreen ribbon around her neck

"That neck has grown in size since yesterday.

From what has been stated above, it is seen that the thyroid in the female is most prone to enlarge at those times at which there is an increased functional/

al strain on the organs of generation.

The question which naturally presents itself now is:- Do we find anything analogous to this in the male?

In endemic centres, goitre in the male tends to appear at puberty and to increase as the sexual organs are coming to maturity; when the function is fully established the thyroid enlargement tends to remain stationary or to diminish in size.

Apart now from the condition of goitre altogether, the sexual organs of the male are functionally much more stable than those of the female; the activity of the testis is perennial, of the ovary intermittent; the testis preserves its function even in old age, the ovary ceases to act at the menopause; the specialist in "Diseases of Women" is a common type, the corresponding specialist in diseases of men does not exist.

From all this the obvious conclusion appears to be:- In both sexes, part of the function of the thyroid is that of auxiliary in some way to the functions of the sexual glands - the ovary and the testis. In the female the thyroid is called upon to bear a greater strain in proportion to the greater instability of the ovarian function and to the more repeated and greater functional strains the generative organs have to bear than in the male, where its activity is less called upon by the more stable testicular function. Exhibit the essential cause of goitre whatever it may be, and what is the result?/

sult? The resources of the thyroid are overtaxed, increased functional activity is called for, and if in certain cases this cannot be supplied without hypertrophy of the gland, then hypertrophy will take place, and naturally most readily:-

- a. At those times where the strain already upon it is greatest - or, in other words, - when the strain upon the generative organs is greatest - i.e. at puberty in both sexes, and during pregnancy, etc., in the female; and
- b. in that sex in which that strain is most constantly kept up and oftenest repeated - i.e. the female.

When the intensity of the infection (again whatever it may be) of the disorder is high, naturally a greater number of men relatively to the number of women become attacked than when it is low, and thus is accounted for the more even balancing between the sexes as regards numbers of affected persons in regions of high intensity of endemicity - as in parts of Switzerland, and North India.

Thus the figures in the following table may be taken as a fair measure of this intensity* in the respective areas:-

* Other data have to be taken into account as well when the intensity of an endemic is being estimated - see below pp.32 and 133.

Locality and date.	Relative proportion of two sexes attacked.			Authority.
	Females.		Males.	
England (average of three lists)	12	to	1	Sir Thos. Watson.
France (1873)	5	"	2	Baillarger
A small Derbyshire village (1769)	50	"	0	Prosser
At Ripon dispensary)	44	"	1	(Robinson
" Chichester " 1885)	34	"	1	
" Pontefract ")	29	"	1	
" Bishopton (near Ripon)	19	"	1	Paley.
" Nottingham (1825)	7	"	1	Manson
" parts of the Himalayas (1912)	1	"	1	McCarrison.

In Acharn, Lochtayside, where the greatest concentration of cases in the Lochtayside area occurs, the population of women to men is roughly 2 to 1.

Social State:

Social state, apart from occupation, has probably little bearing on the actual occurrence of endemic goitre, except in that overcrowding, low living, and other adverse circumstances tend to lower the vitality of the poorer classes, thus rendering them more prone to disease of all kinds.

Occupation:

It is pretty well established that persons whose occupation brings them more or less into direct contact with the soil are more liable to develop goitre, than are/

are others, and this is what one might partly be led to expect from the fact that the condition is essentially a rural in preference to an urban disease.

(v. pp.6, 20, 70)

SECTION IV. B.Etiology.Essential Cause.Introduction, etc.

Although the etiology of endemic goitre is a subject on which amongst observers and theorists there is still considerable diversity of opinion, the trend of modern medical scientific thought seems to be more towards the conception of an Organic causal factor, and away from the previously conceived idea of an Inorganic cause.

The evolution of this Organic theory in its earlier stages was no doubt, in part at all events, contributed to and strengthened by the fact that of the numerous older "Non-organic," as one might in contradistinction term them, theories not one was there which was able to meet all the requirements of the case; geographical and geological causes, peculiarities in manner of living, or habits of the people, etc., seemingly potent in definite districts, failed before the crucial test of general application.

Between the two classes - Organic and Non-organic - however, there is one point in common, and that is the usually observed relationship of the endemic presence of the goitrous condition to certain drinking waters.

From/

From the earlier European times of which we have authentic record, this seems to have been recognised; from the days of Hippocrates and Aristotle (v.p.11), down through twenty-three centuries to the present day there has persisted the belief - which now practically amounts to knowledge - that mainly through the agency of water there is introduced to the interior of the patient some deleterious substance (the idea of the nature of which however has changed again and again) which is the direct or indirect cause of the goitre.

Putting aside for the moment the question whether or not water is the sole vehicle by which the causal factor of the disease is introduced to the system, I shall first of all advance evidence to show that it is at least a frequent one, and then proceed to the examination of those theories which accept this idea as their basis.

Facts which establish a relationship between Endemic Goitre and certain drinking waters:-

Most of the researches into the causation of endemic goitre in Europe have centred around these hot-beds of this disease and the commonly co-existing condition of cretinism, which for long have existed in Switzerland and in the adjoining parts of the surrounding countries, and early in the nineteenth century a considerable amount of literature, which has since become almost classical, upon the subject made its appearance.

Bally, Coindet, and other French army surgeons recorded that they had seen goitre produced in a few days in these districts by the drinking of certain waters(114). Bally has seen it result in from eight to ten days from this cause, and notes of many similar observations are recorded in the French military journals of that period (115).

At a later date St.Lager(73) observed and recorded many instances where in the same village and under the same conditions of living, cases were confined to persons who used certain water supplies, other persons escaping. And it has been stated that frequently, in France, Austria and Italy, men who wish to escape the compulsory military service of these countries, make excursions to certain wells of known goitre-producing qualities, drink thereof, become goitrous, and defy the authorities(50)(116).

St.Lager(74) mentions several of these springs:-

in Maurienne - springs of Argentine, Pontamafray and Villard Clement.

in Briançonnais - springs of Saint Chaffray,

but the value of the statements of their goitre producing qualities as scientific evidence may be called in question as they are not the record of accurate scientific observation, so much as a quotation of expression of popular belief, which, it is well known, is prone to exaggerate.

Recent/

Recent researches by Professor von Wagner in the Carinthian Alps however have resulted in the discovery of a well, the water of which when consumed caused goitre in rats and other animals, and not long ago another well was discovered near Vienna, the water of which produced goitre not only in household animals, but also in the people who drank it regularly(116).

The Durham Goal endemic of 1843-53 (80) is particularly instructive in this connection. During these years the water used in both the food and drink of the prisoners in Durham County Goal was derived from a well, and the men in all classes, whether on low diet or otherwise, suffered extensively from goitre. The connection between the goitre and the water was not suspected till the pumping gear of the well got out of order and filtered water from the river Wear was temporarily introduced. The beneficial effect of the change on the health of the prisoners was so marked, and the disappearance of the neck swellings so immediate, that a sample of the well water was analysed with the result that it was condemned as unwholesome and unfit for use.

Hirsch's extract from the report of the Sardinian Commission is little less striking. At Bozel (Tarentaise) in 1848 there were about 900 cases of goitre and 109 cretins in a population of 1472, while the village of St Bon, standing 800 metres off and at a higher level, was quite free from both diseases, though/

though the condition of life in the two communities was in all respects identical with the exception of the water supply; a water pipe having been carried from the latter village to Bozel, and this water having come into general use, the endemic decreased rapidly, and in 1864 there were only 39 goitres and 58 cretins and no fresh cases occurring.

Then again in 1772, Captain Cook's sailors on their homeward journey having run short of drinking water, gathered ice from the bergs amongst which they were cruising, and melted it in iron pots. Forster, the ship surgeon, stated that all who drank of this water became goitrous, while the others escaped.

The above series of records would seem to establish conclusively that in many cases the presence of goitre is in some way connected with a peculiarity in the drinking water, and the matter would seem to be clinched by the fact that the boiling of the water which exhibits this peculiarity renders it innocuous(2)(66)(116).

Lastly, and possibly most conclusively of all, McCarrison(66) has shown that, where other evidence points to a certain water supply as the vehicle of the causal agent of the disease, if that suspected water be filtered through a Berkefeld filter before use, the goitre in the consumers, particularly if that goitre is not long established, tends to disappear, while, in a number of cases he reports the onset of the condition in previously healthy men subsequent to the oral ingestion/

ingestion of the filter residue (in this way he succeeded in producing the condition in himself); when the residue has first of all been boiled, the disease does not develop.

(Further facts might be adduced in this connection, but a multiplication of data beyond the above, does not seem necessary at this point. Other statements bearing upon the matter are quoted elsewhere in relation to other subjects).

The points now to be considered are:-

1. What is the nature of the impurity or peculiarity in the water which leads to the development of goitre in the consumer? and
2. Can the impurity or peculiarity be introduced into the system otherwise than by the agency of water?

Taking first "the Nature of the Impurity or Peculiarity". A convenient classification of the theories upon this subject is as follows:-

- A. Theories which affirm the Non-organic nature of the impurity and
- B. Those which maintain its Organic nature.

That it is practically impossible, unless perhaps when dealing with the purest spring water, to exclude the possibility of organic contamination from an unprotected water-supply - and most districts afflicted with endemic goitre are districts of unprotected water-supply (country districts are more prone to be the foci of endemic goitre than are towns (v.p 20)). - constitutes/

stitutes a fact which from the onset places Class B in a theoretically unassailable position, where we may leave it while we glance over the now almost discarded Non-organic theories of the much older Class A.

Non-organic Theories of Causation:

Possibly the first definite theory which was ever propounded is that of which we find mention in the writings of Hippocrates and Aristotle, and which for this reason, if for no other, merits a word in passing, though it has absolutely no foundation on which to rest. It is that "Goitre is produced by the drinking of snow water".

With nothing in its favour, this theory is negatived by the facts that goitre occurs in Sumatra, Java, Borneo, and certain parts of tropical South America where this suggested cause does not exist, that it does not occur in Lapland(91), and that in these regions bounding the Polar Seas in which Franklin found it prevalent, it was confined to drinkers of certain river waters, and did not occur among drinkers of melted snow.

The theory, though widespread and popular, cannot be taken seriously, and I at once pass on to others which seem to have a more substantial backing, and up round which a considerable amount of literature has sprung, though nowadays the interest they possess is more historical than scientific.

During the earlier part of the 19th century, most of the research into the causation of goitre was conducted/

ducted along lines which sought a geological solution of the problem, i.e. some geological features of the land, common to all districts afflicted with the condition in its endemic form.

As already noticed (v.pp.42-43) Bally(115) observed that in certain parts of Switzerland users of certain well waters were more liable to be affected than were users of other waters. This he ascribed to the impregnation of the well water with calcareous or other mineral matter, and Coindet's (10) observations in Geneva that persons drinking certain hard pump waters were oftenest attacked, supported this theory.

Manson (Nottingham, 1825) was inclined to put the condition down to the same cause(10), and Johnston's report on the Durham Goal-water (v.Appendix B.) seemed to afford further corroboration.

It has also been shown that in districts of Bari Doab in the Punjab, where goitre affects 60% of the population, there is a boulder gravel subsoil, and 59 grains of lime have been found to the gallon of water(117).

In addition to calcium salts the salts of magnesium in some form or other have been considered by many to play an important part in the matter. It was primarily due to the extensive geological enquiries of Grange(118) and the analyses he made of the waters of the Isère (a river rising in the Mont Blanc range and flowing into the Rhone) that these came to be looked upon as active agents in the production of goitre,* and/

* Latterly Grange discarded the theory himself (75).

and on investigation, further evidence in support of this point was forthcoming from the Alps, Pyrenees, Dauphiné, parts of Brazil and Russia.

Perhaps the strongest prop however on which this - the dolomite or magnesian limestone - theory rests, is the table drawn up from McClelland's (40) investigations over an area of more than a thousand square miles of territory in North India, its strength lying in the fact that in every position of this area the same geological circumstances attended the presence or absence of the disease:-

Water derived from	% of population affected with Goitre.
Granite and Gneiss	0.2%
Mica, Slate, and Hornblende	0
Clay Slate	0.54%
Green Sandstone	0
Limestone Rocks	33.0%

In England a high intensity of endemicity has already been seen to prevail over the Carboniferous limestone of the Pennine Range, etc. (v. p.26), and, as has already been stated, the rocks of the Loch Tay endemic area contain both lime and magnesia (v. pp.9-10).

Such in brief is the evidence in favour of the most important of the geological theories.

The case against may be summarised in several short sentences.

1. The disease frequently prevails in districts where Calcium and Magnesium are absent or almost absent from the geological formation:-

Thus, analyses of the waters of the following goitrous regions show an absence of Magnesia:-
 Rheims (Maumené), Auvergne (Bertrand), Lombardy (Demortain). For further examples St. Lager's "Etudes" (77) may be consulted.

Again, after analyses of specimens of the drinking water within a radius of ten miles of Bhagsu (Dhurmsala, India) where goitre prevails extensively Wilson (119) reported that only three showed traces of lime, and none gave any evidence of magnesia or iron.

2. The disease is frequently absent from districts where Calcium and Magnesium Salts abound:-

Thus it is comparatively rare in New Zealand, which is largely composed of Magnesian limestone (49), while it is absent in the Peshawur Valley in Rajpootana, and in Central India where for the most part the water contains even more lime and magnesia than does that of other districts where goitre more or less generally prevails (54).

3. Endemic goitre is subject to seasonal and cyclial fluctuations in prevalence.

In India, where the phenomenon is most pronounced, the Seasonal increase in prevalence coincides with the/
 the/

the rainy season, when the inorganic constituents of the soil are in a greater state of dilution than at other times(53). The probable explanation of this occurrence is discussed below (v.p.58)

4. Sometimes, in neighbouring villages, communities existing under similar conditions as to rock and soil, elevation, etc., one village may be affected with the disease and the other escape (78)(25).
5. The therapeutic administration of magnesium and calcium salts, even over a prolonged period of time, does not produce goitre.

The failure of the calcium and magnesium theories to meet all cases, has led observers to seek further for the causes of goitre, and other theories of a geological nature have been advanced from time to time.

Neither Chatin's theory, based upon investigations conducted in various goitrous countries, that the condition is due to the presence of minute quantities of Iodine in the drinking water or in the air, nor its converse - that it is due to the absence of iodine - has received any support, and other substances such as silica, fluorine, carbon dioxide, oxygen, radium (56), etc., have been suggested only to be dropped.

St Lager (76), a French writer who accumulated a vast amount of evidence upon the subject, found that goitre-producing waters were not of necessity hard as proved by the soap test) and revived the theory of Paracelsus/

sus (v. p.11-12) that endemic goitre was caused by the presence of iron pyrites, or, less often, the sulphides of copper and other metals, in the water. To explain his theory in the face of the fact that iron sulphide is insoluble in water, he argued that in those areas where the salt existed as magnetic pyrites, a form readily convertible into the sulphate of iron, there the endemicity was most marked; and to reconcile the theory with the frequent coincidence of endemic goitre centres with dolomite formations it has been stated that metaliferous earths exist almost without exception in the neighbourhood of magnesian limestone formations.

Against this theory are ranged the same set of facts which upset the Hard-water theories:-

1. The disease may prevail extensively where the suspected minerals are absent, though, owing to their very wide distribution, such districts are rare:- as in Bhagsu(India)(119).
2. The disease may be absent from localities where these minerals abound:- as over the Lias formation which extends from Teesmouth to Lyme Regis in Dorset, and contains much iron pyrites (v. p. 25).
3. Iron Sulphide is not given as such therapeutically, but where other preparations of iron are given, there is generally a constant supply of the sulphide in the the black deposit which is formed on the tongue and teeth, not to speak of the quantity which passes through the colon (as shown by the black discolouration/

tion of the faeces). Notwithstanding this, I have been unable to discover notes of a single case of thyroid enlargement traceable, or even ascribed to this cause; indeed iron is frequently administered with benefit to anemic girls suffering from goitre.

Lastly as regards geological theories, Ferguson(26) in exploring the goitre affected districts of Se Chuan in Lololand, on the Chino-Tibetan frontier, noticed that it was in valleys, the surrounding mountains of which were largely composed of mica schist, that the disease was commonest. His view, that the condition owes its origin to the mica which is washed down by the melting snows and is present in the drinking water, is disproved by McClelland's table (v. p. 49) and by the fact that extensive areas of mica schist are found in parts of the world where goitre is rare or absent.

An unbiased study of the pros and cons therefore of these several theories leads one inevitably to two conclusions:-

1. Goitre in its endemic form is independent of geological influences so far as concerns the actual "causa vera", and:
2. The evidence collected by the advocates of the geological theories can only be taken to show that over certain soils the condition appears to prevail more than over others.

(St Lager in his "Etudes sur les causes du Cretinisme/

"Cretinisme et du Goitre Endemique" quotes some forty theories of causation, both "water-borne" and otherwise, which have been propounded from time to time, therefore it may be well here to extend our survey to include a few of these, in addition to those already reviewed, before passing on to discuss the Organic theories as advanced by modern investigators, and on which much of the present day interest is centred.

As a sample may be taken those which group themselves under the heading "Air-borne":-

Rarity of Atmosphere.	Cold and dry air.
Air holding too little oxygen.	Action of cold air on the neck.
Air holding too much oxygen.	Air charged with electricity.
Air containing miasm - - paludal or special.	Want of electricity in the air.
Air charged with sulphurous vapour.	Hot air, damp air.
Want of iodine in the air.	Changeable air, stagnant air, etc., etc.

A glance over the Geographical Distribution of the disease (v.pp.14 et seq.) giving attention to the elevation, surface configuration, latitude, etc., of the different centres, is sufficient to show the fallacy of all these theories.

A few others of the many are:-

The eating of oatcakes (Good) (10)	Low living
Bad food	Overcrowding
Scarcity of food	Paucity of solar light
The carrying of weights on the head (Thurston).	The playing of wind instruments (5), etc.

As/

As essential causes, all of these may be at once discarded; as predisposing and abetting factors some have already been examined (v. p.39) and others will be examined later.)

Organic Theories of Causation:

Throughout the "Geological Epoch" there was running an undercurrent of doubt, and many observers and critics of observers in this period certainly held that "hydrotellurique" (in the sense as originally used by St Lager) influences did not adequately account for the existence of all endemic centres, but it was in the last quarter of the 19th century before the suggestion that possibly an organic agent might be in operation at the root of the trouble became anything more than a suggestion.

Certainly Saunders(57) in 1789 conjectured that goitre might owe its origin to some organic substance, peculiar to the waters of these regions where it existed endemically, and suggested that "an accurate analysis of the water used in common by the natives, where the disease is more or less frequent, and where it is not known, in similar exposures, might throw some light on this subject", but the first definite Organic theory which has come under my observation is that of MacNamara (55) who, as a result of extensive investigations in Himalayan and Sub-Himalayan India, rejected the lime and magnesian theories and, in a book of 500 pages, submitted and adduced much evidence in support of his view that/

that goitre was caused by some low form of living organism, the exact nature of which was conjectural but appeared to have a common origin, under certain con-joint conditions of soil and climate, with those of malaria, dysentery, cholera, etc., and suggested that the disease might prove amenable to the same sanitary measures, could these be carried out.

Again, Blake(49) in 1894 stated that "Common to all cases (of goitre) is some organism or some organic poison", the nature of which he does not indicate beyond suggesting that it is "possibly protozoic, i.e., animal rather than vegetable, as it follows water-lines and can induce adenoid proliferation."

In some text-books on Hygiene and Public Health of a still later date the possibility is not even mentioned, while, writing on Endemic Goitre in 1902, Murray(2) dismisses opinion on this aspect of the subject in the sentence:- "What the active constituent of the water may be is not yet known, but the fact that such water is rendered harmless by boiling, indicates that it is possibly a living micro-organism".

The mere fact that the water is rendered harmless by boiling is insufficient evidence on this point, as boiling, by precipitating the carbonates held in solution by the dissolved carbonic acid, reduces the total hardness (which has been shown to have been considered a cause of goitre) by removing the temporary hardness- still, as Murray states, the fact may also be taken to/

to indicate that there is "possibly a living micro-organism" present, and to be reckoned with.

It falls to us therefore now to discuss this proposition:- "The essential cause of endemic goitre is some organic substance". After which it will be necessary to determine if possible:-

- A. The exact nature of this substance; and,
- B. The manner of its action in the production of the disease.

1. The essential cause of endemic goitre is some organic substance.

The first significant fact suggested by a review of the evidence already set out in this thesis is as follows:- Endemic goitre shows a predilection for mountainous districts, and in these districts is principally confined to deep, sunless valleys (v.p.21). Thus, in the Loch Tay area almost all the cases occur on the south side of the loch, where the hill slopes are for several months of the year almost sunless. On the north side of the loch, where the sun exerts its full influence, cases, as stated, are rare.

The point of this fact in the present connection is obvious, when one recollects the well-known sterilising action of sunlight.

Secondly, the Seasonal and Cyclical Fluctuations in certain endemic centres already referred to, point distinctly to an organic causal agent.

Under "Seasonal Fluctuations" the following observations/

tions are noteworthy:-

- a. In Himalayan India it is rare or unknown for a case of goitre to arise in the winter months, when the atmospheric temperature sinks to freezing point, while existing goitres tend to diminish. New cases do not arise between June and September, when the shade temperature rises to 103° - 110° F. (65).
- b. E. Bircher, in experimenting upon rats, convinced himself that goitre-producing water is potent in the summer and non-potent in winter (Swiss summer temperature is about the same as that of Indian spring and autumn).

The inference from these data is that, as no inorganic substance can conceivably depend for its action on the variations of temperature in such a manner as above described for the goitre-producing agent, and, as the potency of this agent varies with the temperature, much as the activity of micro-organisms is found to vary, viz:- inhibited by cold and excessive heat, and most active at moderate temperatures, the said goitre-producing agent is most probably of an organic nature. This is supported by the fact that:-

- c. In the goitrous districts of the Himalayas it is during and after the rains that the disease most commonly begins, and most rapidly develops (53).

At these times the water supplies become flooded with washings from cultivated land, i.e. they are more highly charged with organic matter than, than at other times./

times.

This Seasonal Fluctuation of goitre is analogous to that observed in connection with certain other diseases which may exist endemically, and are now definitely known or admitted to be of organic origin, as enteric fever, summer diarrhoea, etc.

"Cyclical Fluctuations":-

Many cases are on record, where endemic goitre has made its appearance in localities where it was previously unknown, as in Savoy and Ardennes (Baillarger)(45), Nagar(65), etc.

There are on record also numerous cases in which villages and districts which have at one time been afflicted with the disease are now almost exempt. Thus, the centres referred to in Barton's monograph (53) and in Hirsch's "Geographical Pathology" no longer exist (3). The tendency seems to be for goitre to increase in an infected locality, till a point of maximum intensity for that locality is reached, when it gradually diminishes. This is shown by Baillarger's(45) observations on the variations of the endemic in sixty Departments of France, as demonstrated by the figures given in the recruiting tables for the fifty years 1816-65. He found that the endemic had increased in twenty-six departments, remained stationary in seventeen, and decreased in seventeen, and, what is most important, fifteen out of the seventeen in which decrease took place/

place were amongst the most goitrous districts of France.

In many instances this can be traced to a change in the water supply, as in the case of the village of St Bon (v.pp.44-45), but in some cases, particularly where the decrease takes place almost simultaneously, though gradually, over wide areas, other factors must be sought for.

The two forces which may operate to bring about this end are:-

- a. A gradual diminution in virulence, or gradual dying off of the goitrogenous agent, and,
 - b. A gradually acquired immunity on the part of the people.
- a. A gradual diminution in virulence, or gradual dying off of the goitrogenous agent:-

In the neighbourhood of Auchterarder and Aberuthven, in Perthshire, where goitre used to be very prevalent, the condition is becoming gradually rarer (of this I am assured by doctors who have practised in the district for many years). This is more probably due to a gradual decrease in the activity of the goitrogenous agent than to an acquired immunity, as the condition was never sufficiently widespread or intense, to produce an immunity so perfect, even were such an immunity definitely proved to exist elsewhere; and it is obvious that the presence of no Non-organic substance can vary in/

in such a manner as to explain the phenomenon. (v. also Baillarger's figures, etc. p.59).

b. A gradually acquired immunity on the part of the people:-

In the villages of Gilgit (Kashmir) McCarrison(65) has found that the condition is rarely observed in children under two years of age, whereas in a few villages of Chitral a high proportion of young children is affected, some even while at the breast. He suggests that the difference may be due to an acquired immunity in the children of villages where the endemic has prevailed for centuries - an immunity which may be sufficient to protect them until the critical age of puberty is reached.

To me this argument appears somewhat strained, and against it is the fact that an attack of the disease is not protective, for frequently a patient who has got rid of the condition subsequent to a removal from the affected district, suffers from a recurrence of it on his return, even after a short residence away. It seems rational to contend that, if attacks of a disease in his or her progenitors can render an infant immune to that disease, an actual attack of that same disease should be sufficient to build up in an individual an immunity strong enough to render him or her safe from another attack for at least a considerable time.

Still, should such an immunity be proved to exist for goitre, it merely strengthens the argument in favour of an Organic cause, while its absence does not negative the/

the probability, for science already recognises certain diseases, Organic in origin, where no immunity follows an attack.

In making out a case of this kind which would place the cause of endemic goitre as Organic, and the disease therefore as probably infectious, one is justified in asking whether the condition is capable under any circumstances of taking on an epidemic form.

Before seeking an answer to this question it is well to remember that if an affected person leaves an endemic locality before the thyroid has passed the early stages of pure hyperplasia (v.p. 74) the enlargement tends to disappear usually in a short period of time - thus proving:-

1. that a constantly renewed supply of the poison is required to maintain the enlargement, and
2. that, if the poison is actually the product of a living organism, that organism is incapable of surviving, at all events in an active form, for more than a short time in the human body.

With these considerations before us, it is obvious that goitre cannot give rise to rapidly spreading extensive epidemics in previously healthy localities as may plague, cholera, etc.

That epidemics do occur, and in a manner which supports the hypothesis of an organic causal agent, is conclusively established:-

It will suffice to quote one or two examples:-

1./

1. The miniature epidemic which occurred amongst Captain Cook's sailors has already been noticed (v. p.45).
2. Guillaume (4) reports a school epidemic in which 161 out of 350 boys and 245 out of 381 girls were attacked.
3. McCarrison (65) records the occurrence of an epidemic which broke out suddenly amongst the boys in the Bishop Cotten School at Simla, and attacked also some of the masters without any change having been made in the water supply, and without any appearance of goitre amongst the other residents of Simla.

Usually in schools the epidemics last a few months and die out after the holidays (4).

(For further records of epidemics v. St Lager's "Études" pp. 223-230).

Before passing on to discuss the exact biological nature and mode of action of the causative agent, when still further evidence will be submitted, it is well here to re-examine one or two points which arose during my criticism of the Non-organic theories:-

1. Certain mineral constituents of the soil in affected areas were believed to bear a causal relationship to the occurrence of the disease in its endemic form. It was found however that the condition was often present when these soil constituents were absent, and vice. versa.

This disagreement between suggested cause and effect, and which is fatal to the theory, vanishes if for/

for "certain mineral constituents of the soil" are substituted the words "some substance of an Organic nature".

2. Certain villages in affected areas similarly situated as regards rock, soil, elevation, habits of people, etc., etc., vary in degree of endemicity - indeed one village may show high intensity of the condition, and another near by be exempt.

Here too the conception of an Organic causative agent at once throws light upon the darkness left by an attempted explanation under the Non-organic theories.

II. According to the plan above laid down, the next matter to be discussed is "The exact biological nature of the Goitrogenous Agent".

Unfortunately in the present state of our knowledge there is little definite that can be said on this subject.

MacNamara's (55) theory of a possible relationship as regards a common origin between goitre, malaria, cholera, and dysentery, was conceived before an accurate knowledge of the specific nature of these three latter diseases was arrived at, and has therefore not stood the test of more modern investigation. It is of interest however to note that in 1898 Grasset (61) published an account (not confirmed by the Swiss Goitre Commission and other observers who gave special attention to this question) of a hematozoon which he found in the peripheral blood of persons who exhibited goitres of ten to/

to fifteen days standing.

In this connection too, the "Parasitic Thyroiditis" recently described by Chagas (59) merits mention as, according to him, the disease, which is endemic in Brazil, frequently produces a condition indistinguishable from endemic goitre. The specific organism - a trypanosome - the "Schizotrypanum cruzi" is conveyed to man by biting insects - "Conorrhinus Megistus" (Chagas) and "Cimex Lenticularis" (Brumpt). The disease affects infants chiefly, and amongst them is responsible for a high mortality. During the acute stage, while the trypanosomes are found in the blood, there is pain in the thyroid, elevated temperature, nervous symptoms, and enlargement of liver, spleen and lymphatic glands. When the trypanosomes disappear from the blood this stage passes off, and the chronic form of the disease tends to develop; the thyroid enlarges (sometimes enormously) and other symptoms may arise, viz: nervous symptoms, heart symptoms, and slight bronzing of the skin; should however these symptoms not arise, a condition, as has been stated indistinguishable from true endemic goitre as it occurs in Europe and Asia, results.

Though the two conditions are essentially different, it is important, as McCarrison (67) points out, to remember

1. that the causes of all endemic thyroid enlargements are not necessarily the same, and

2./

2. that a form of endemic thyroid enlargement can be conveyed to man by biting insects, and
2. that there is a possibility of two form of enlarged thyroid existing side by side endemically in the same locality.

As the result of recent experiments, E. Bircher has advanced the theory that the actual cause of endemic goitre is a colloid substance present in the water of goitrous localities. This colloid is stated to be produced by an organism which exists in the soil, and which is itself responsible for the production of cretinism.

McCarrison (66) however criticises Bircher's findings and holds that the real source of the trouble is an organism which is actually in the intestinal tract of the sufferer. He has isolated a spore-bearing bacillus from the faeces of goitre patients which exercises a curative influence when employed as a vaccine. This however is insufficient to confirm the organism in question in the role of specific virus of the disease, for it is found that autogenous coli vaccines and also non-autogenous staphylococcus vaccines exert a similar influence (v.pp.114,115), the inference from which would seem to be not that any one of these organisms is the "causa vera" but that, where the action of these is combated by vaccination, the thyroid is relieved of a considerable amount of work and is enabled to/

to cope with the specific virus without hypertrophy.

As stated above, Blake (49) remarked in 1894 that in origin the disease was probably organismal, and possibly protozoic (i.e. animal rather than vegetable) in that it follows water-lines and can induce adenoid proliferation. This view certainly appears to be supported by the lymphocytosis (109) and eosinophilia which are found to occur in cases of endemic goitre (v. pp.81,82) and observers have recorded from time to time the discovery of amoebae (110) in the intestine of sufferers, though it has not been found possible as yet to prove the specificity of these forms.

Recently Graf, as the result of experiments which he has been conducting, has expressed the opinion that the causative agent is an albuminoid body. As a full account of his work has not yet (to my knowledge) been published, criticism must be withheld for the present.

III. Sufficient has been stated to indicate that while evidence as to the exact biological nature of the goitrogenous agent is suggestive, it is still inconclusive, and while this is so, it necessarily follows that any account of the Mode of Action of this agent must be so likewise.

Blum (83) in 1900 stated that goitre was due to the presence of a living excitant in the intestinal canal, but he adduced little in support of his contention. The following subsequently accumulated evidence however points to the truth of his view:-

1. In fishes the thyroid communicates with the pharynx by means of a duct, an indication that probably the secretion, which is anti-toxic and bactericidal in its action, is intended to exert this action, in part at all events in the alimentary canal. This is supported by the fact that trout which are confined in filthy unhygienic tanks, tend to develop goitre(82), probably because the increased activity which is the first reaction of the gland to excitation, tends to be followed by retention of colloid and degenerative changes, which result in the production of goitre.
2. Thymol, which is a powerful germicide, and which, owing to its comparative insolubility in water (1 in 1500), is probably only slightly absorbed from the alimentary canal, has been found to have a remarkable effect in curing or improving recent goitres, and sterilisation of the gut of recent goitre patients by the action of the lactic acid ferments, in the form of the bacillus Bulgaricus in milk, has been followed in a high proportion of cases treated by strikingly beneficial results (67).

The obvious inference from this would seem to be, as McCarrison points out, that the source of the trouble is located in the alimentary canal, though it may be contended (and fairly enough I think) that what occurs here is on a par with the result obtained by vaccination (v. above) i.e. the thyroid being relieved of part of/

of its normal work, is enabled more freely to cope with the noxious products of the specific virus.

3. The blood changes (v. p.81) in endemic goitre point to the intestine as the source of the infection.

4. As stated above, vaccines of organisms which habitually are found amongst the intestinal flora, exert a curative influence on the disease.

The evidence is therefore fairly strong, though not absolutely conclusive, that the enlargement of the thyroid in the initial stages of goitre is a purely protective hypertrophy, due to an increased call made upon the gland for anti-toxic substances to combat the poisons circulating in the blood, and proceeding from some substance or substances of an organic nature present in the alimentary canal. This early hypertrophy is followed by the retention of colloid and degenerative changes, resulting, in the various stages, in the different types of goitre described below (Section V).

The second question propounded above, still remains to be answered, viz:- Can the goitrogenous substance be introduced into the system otherwise than by the agency of drinking water? The report on the epidemic outbreak in the Bishop Cotten School at Simla (v.p.63) would indicate that this may occur, and the fact that in certain parts of New Zealand endemic goitre exists amongst persons who drink only the water from boiling springs (66) points in the same direction.

Further/

Further, McKenzie (33) states that the towns of Larkhall and Bothwell have had, for sixteen years prior to 1899, the same water-supply, no water being introduced into Bothwell other than from the same source as that of Larkhall; yet in Larkhall goitre is endemic, while in Bothwell it is absent.

St Lager and others have quoted instances in which the drinking of water rendered innocuous by boiling or distilling has been insufficient to secure immunity in the case of persons living in goitrous localities.

McCarrison (64) who in 1904-5, as the result of experiments conducted upon lines thus indicated, was able to satisfy himself that the disease could be neither cured nor prevented by this means, so long as the possibility of infection from the soil was not excluded.

The most probable explanation of these and similar instances is that soil is also a vehicle of the goitrogenous substance, and in support of this, stands the fact that those persons whose work brings them into frequent and close contact with the soil are most liable to become affected - thus, McKenzie (34) found, in the North Lanark endemic area, that 98% of the cases occurred in the mining and labouring classes, and McCarrison (65) has noted a similar preponderance of cases amongst the soil cultivators in Gilgit and Chitral. Likewise, in this connection it is of interest to note that, amongst the lower animals, the condition is most often met with in herbivora (v. p.26.) (Curiously enough Marine/

Marine finds that in endemic centres where goitre occurs in fish, only carnivorous fish are affected).

Recently extensive studies by military surgeons, especially in the south of Austria, have led to the development of a Theory of Contagion or direct case to case infection, and cases in which the agency of neither soil nor water could be traced and which therefore seem to support this view, have been reported by McCarrison (68) and Von Kutchera (116). It is possible that genuine cases of direct infection do occur and it is rational to expect, from the evidence already detailed of the organic and infective nature of the condition, that they sometimes must occur. Taussig (84) stated that he believed infection might be by the saliva, but as yet there appears to be insufficient evidence to establish his point, and from the comparative rarity of instances of this nature (i.e. - suggestive of contagiousity) one can consider them as of only small practical moment, though from an etiological standpoint they are of extreme interest and importance.

It is of interest to remember in connection with Taussig's view that an association has been described between caries of the teeth and endemic goitre. A similar association has been noted between this condition of the teeth and certain other thyroid conditions i.e. exophthalmic goitre and myxoedema (Murray).

To revert to the common though not universal association/

association of endemic goitre with hard water districts it is probable that this association, which is too frequent to be entirely accidental, may be due to the fact that in such districts the soil is more porous, and therefore more liable to retain organic pollution, than in other districts. It is also possible that the presence of lime, etc. in the water may in some way render the bowel a more suitable habitat for this causal organism, or that lime, etc., in the soil may render that soil more suitable for its growth outside.

These points however require further elucidation, and at present one does not seem justified in drawing from the facts and arguments above set forth more than the following deductions regarding the goitrogenous agent:-

1. It is organic in nature.
2. It exists in the soil and is usually introduced to the system of the individual by the agency of water, though occasionally by other means.
3. Its seat of activity in the affected individual appears to be the bowel.
4. It is slow-growing and readily dies out or becomes inactive in the individual, i.e. a continued supply of the goitrogenous substance is required to maintain the thyroid enlargement (that is prior to the occurrence of fibrous and other permanent changes in the gland).
5. Its activity, though not dependent on, is enhanced in some manner as yet not fully understood, by the presence of lime or magnesia in the soil and in the water supply.

SECTION V.Pathology.

The pathological changes met with in cases of true Endemic Goitre may, in the light of our present knowledge, be described under the following heads:-

- I. Pathology of the Thyroid Tumour.
- II. Alteration in the Iodine content of the gland.
- III. Hematological Changes.

after which the probable pathogenesis of the condition will be considered.

Pathology of the Thyroid Tumour:

Before detailing the changes met with in the thyroid it may be well here to resume the normal characteristics of the gland in its adult, infantile, and foetal types respectively:-

Adult Thyroid.	Infantile Thyroid.	Foetal Thyroid.
Follicles regular in size and shape	Follicles less regular in size	Follicles less clearly marked and appear as clumps of cells
Follicles almost always round in shape.	Follicles almost always round in shape.	(larger than in infantile type) amongst newly formed connective tissue.
Follicles lined by single layer of cubical epithelium and separated by normal connective tissue.	Cells of epithelial layer larger, more granular, and in more than a single layer.	
Follicles uniformly packed with colloid.	No colloid in follicles.	Colloid absent.

Types of Goitre (endemic):

Parenchymatous or Simple Goitre.

Simple Fibrous Enlargement)	(From the develop-
)	ment of various
Simple or Primary Cystic Enlargement)	(secondary changes
)	(in Parenchymatous
Simple Fibro-Cystic Enlargement.)	(or Simple Goitre.
)	
Secondary Cystic Enlargement.)	

Adenomatous or Cystic Adenomatous Enlargement.

Vascular Enlargement.

Congenital Goitre.

a. Parenchymatous or Simple Goitre:

The first stage of thyroid enlargement in endemic goitre - a soft compressible enlargement common in young adults, particularly girls - is a true hypertrophy or hyperplasia, i.e., an exaggeration of the normal structure, an equal hypertrophy of all the normal constituents of the gland - an increase of the gland elements and also of the fibrous tissue. The increase in volume is usually bilateral and preserves the shape of the gland, though it may be irregular, owing to the separate affection of one or other lobe, or the isthmus.

Occasionally in the thyroid there is an accessory lobe; this, like other parts of the gland, may be the seat of goitrous enlargement, and in rare cases secondary growths resembling hyperplastic thyroid tissue in structure have been noted elsewhere in the body, as on the vertex of the skull, in internal organs, etc., of goitrous patients. Such cases have been recorded by/

by Morris, Howard, and Neumann*.

On section the cut surface has a somewhat coarser appearance than normal, and microscopically the vesicles are increased in size, and contain much viscid secretion.

(This is to be distinguished from physiological non-endemic goitre which is a compensatory histologically-normal hypertrophy of the glandular tissue called forth to meet the increased demand for thyroid secretion as it occurs particularly in certain women during menstruation, pregnancy, labour, flooding in childbed (23) etc.(v.p.35). This is not true goitre and is usually of temporary duration. In endemic centres however, persons liable to this form of thyroid enlargement are particularly prone to develop true goitre). Parenchymatous or simple goitre may become fibrous or Cystic according as there is disproportionate over-growth of fibrous tissue, or enlargement and coalescence of vesicles. More usually there is a combination of these two changes, resulting in the production of the fibro-cystic variety.

b. Simple fibrous Enlargement:

Here there is hypertrophy and round celled infiltration of the fibrous framework of the gland. This may be local or general, but usually commences in the deeper parts of the gland, extends thence towards the surface, at the expense of the follicular structure, and/

* It is of interest to note here in passing that secondary deposits after primary malignant disease in the thyroid reproduce the type of thyroid tissue.

and produces a hardening of the affected parts. There is a tendency for this fibrous tissue to contract and even obliterate some of the vesicles.

c. Simple or Primary Cystic Enlargement:

(An uncommon condition). Here the tumour is filled with little primary cysts, due to the formation of the colloid content of the vesicles outstripping the absorption, or possibly to the fact that the colloid has undergone some change, which renders its escape from the vesicles via the intercellular channels of Hürthle to the lymphatics difficult or impossible, the resulting retention acting further in the same direction as a radially exerted pressure tending to close these channels. In this connection too the physiological hypothesis, that the increase of colloid simply represents increased production and storage of secretion in the gland consequent upon an increase of toxic substances in the blood, is to be remembered; indeed I think it probable that this last is the true explanation*, though possibly there may be also a certain amount of retention for:-

1. the colloid is not of the same viscosity in all goitres.
- 2./

* Recently Wooley(128) stated that as the thyroïdal colloid, being gelatinous, viscid and non-diffusible, could as such have no physiological value and suggested that as colloids can be converted into crystalloids without alteration of their chemical nature herein may lie the solution of the problem of the resorption of the thyroïdal colloid, the consequent theory of the increase of colloid in certain goitres being that the cells may produce under certain abnormal circumstances substances which prevent colloidal transformation, or that the bloodstream may bring substances which prevent the normal changes.

2. were the constant pressure of the colloid sufficient in itself to obstruct the intercellular channels, one would expect to find atrophy of the secreting epithelial cells under this pressure even in early goitres.

3. it is not definitely proved that the only means of escape from the glands open to the colloid is via these channels; besides which colloid has been found lying free in the blood vessels of certain forms of goitre(v.p.79)

The single layer of cubical epithelium which normally lines the follicles, tends to show marked cell proliferation, and may form cell groups projecting into the colloid, the cells being enlarged, irregular and markedly granular.

As these cysts continue to enlarge the original lining, epithelium tends to degenerate, and the cysts may coalesce, forming secondary cysts of various sizes.

The contents of the cysts may be a watery fluid, but more usually the colloid persists - sometimes more or less inspissated - as a dull yellow or brownish viscid substance containing often fatty matter, tablets of cholesterine, and occasionally calcareous particles.

The walls tend to become smooth, but may contain calcareous deposits; generally a certain amount of the original secreting epithelial lining remains, and may be recognised, the cells being sometimes columnar and sometimes flattened.

d. Simple Fibro-Cystic Enlargement:

This is a combination of the two preceding types, and its nature may be inferred from the descriptions of these. Here the cyst walls are supported by the proliferated fibrous stroma, which may become cartilaginous and is occasionally calcified.

e/

e. Secondary Cystic Enlargement:

This form of goitre may arise from mucoid softening of the swollen parenchymatous tissue. The contents of cysts of this nature may resemble that of the simple cysts already noticed, or may become changed with greyish granular pulp which may become calcified.

The walls of these cysts are generally rougher and more rigid than those of primary cysts.

f. Adenomatous or Cystic-Adenomatous Enlargement:

Adenomata - i.e., individually encapsulated masses of thyroid tissue of foetal type - constitute a common form of goitre. As a rule this begins early, according to Da Costa (6) before the fifteenth year, and is particularly prone to become cystic, the fluid which forms being due to mucoid liquefaction of the proliferating epithelium. The lining membrane of these cysts frequently gives rise to papillary ingrowths, showing a low form of malignancy.

As a rule single-cysted goitre is due to the presence of a cystic adenoma in one lobe of the gland.

g. Vascular Enlargement:

There is sometimes met with a form in which the increase in size of the gland is due to dilatation of the blood vessels with intercommunications, the veins often forming dense knotted plexuses or spongy masses of large venous spaces.

The glandular tissue shows no new formation, but
on/

on the other hand usually loses its granular texture and becomes flabby and dark. According to Guttnecht (35) this type of goitre develops from a hyaline or colloid degeneration of the tissues.

McKenzie (35) reports having found in such a goitre colloid lying free in the lumen of the bloodvessels.

h. Congenital Goitre:

This may be parenchymatous or cystic and does not differ from the corresponding adult type.

Some cases are still-born and an occasional association with hydramnios has been observed.

Thus, in connection with the two simple types of goitre, viz:- Simple Parenchymatous Goitre, and
Adenomatous Goitre,

certain secondary changes may occur. Those already mentioned are as follows:-

1. Fibrosis or cirrhosis of gland, sequel of round-celled infiltration.
2. Central cicatrisation of fibrous tissue with obliteration of vesicles.
3. Colloid increase and colloid degeneration.
4. Cell proliferation of lining epithelium of vesicles.
5. Degeneration of lining epithelium of and coalescence of primary cysts.
6. Calcareous deposits on or in cyst walls.
7. Cartilaginous change in cyst walls.

8. Local necrosis into soft mucoid masses which may become calcified.
9. Cystic degeneration of adenomata.
10. Formation of vascular goitre.

In addition to these, the following secondary changes may occur:-

1. Hemorrhage into the substance of the gland.
This is rare and is usually the result of some injury.
2. Hemorrhage into a pre-existing cyst. This is common and the contents of these cysts often contain altered blood.
3. Obliteration at the capsule of entering vessels may produce local degenerations into pulpy sebaceous masses.
4. Inflammation)
5. Suppuration) very rare.

Alteration of the Iodine content of the Gland:

From the facts I. that the normal adult gland of man and animals contains 0.3 - 0.9 m.g. iodine to the grm. of dried substance (the iodine is present only in the colloid substance); and

II. that the healthy thyroid gland of the foetus and the new-born child contains no colloid and therefore no iodine - it has been supposed that the gland is the body's storehouse of iodine, and that the amount of iodine present in the gland may be taken as a measure of the amount of that substance taken into the/

the economy whether in food or as a medicament (125).

In true parenchymatous goitres, purely fibrous goitres, and portions of goitre which have undergone cell degeneration, there is no iodine or, at least, very little. On the other hand, goitres containing much colloid are rich in iodine but, according to Oswald, where there is marked colloid degeneration the proportion of iodine decreases and may disappear altogether.

Haematological Changes.

Grasset (81) in 1898 described a haematogoon which he found in the peripheral blood of sufferers from goitre of ten to fifteen days standing, but, as already stated, (v.p.64) his account has received no substantiation from other investigators who have paid particular attention to the subject. In goitre patients however there are generally definite blood characteristics to be met with, and a good many years ago Holland(86) described an excess of pale cells and a peculiar alteration of the red cells.

Millar has found in cases of simple goitre an absolute reduction of polymorphonuclear neutrophilic leucocytes down to 50% of normal, with an increase of lymphocytes of from 30% to 50%, and McCarrison(67) gives the following figures as the result of blood-counts in seventy-three cases at all stages of the disease:-

Polymorphonuclear neutrophilic leucocytes	-	Below normal in 98.9% of cases
Small mononuclear leucocytes (lymphocytes)	-	above normal in 92.5% of cases.

Eosinophilic/

Eosinophilic cells - above normal in 88% of cases
 (In blood taken direct from the thyroid gland by a hypodermic needle large numbers of eosinophilic cells were found.)

Large mononuclear leucocytes - above normal in 23% of cases.

Morone (87) in 1910 described a lowering of the Haemoglobin Index and of the total number of red corpuscles, while Lidsky and Kottmann (67) have found that the coagulability of the blood is increased.

(Similar changes have been found by Falta and Berterelli (126) in the blood of adult animals after thyroidectomy).

Probable Pathogenesis of Endemic Goitre:

The following sketch of the probable pathogenesis of endemic goitre is largely based upon the theory of the anti-toxic action of the thyroid secretion as advanced by Baumann and his pupils and, more particularly by Oswald. Recently two other theories of thyroid action have been advanced viz:- the Single and the Double Hormone theories, the former of which suggests that the thyroid produces its various actions by a single thyroid hormone acting primarily upon the central nervous system, and the latter that there are either two hormones, one disassimilatory and the other assimilatory, or a single hormone producing these actions according to the apparatus influenced. Even accepting one or other of these theories however, it is probable that the/

the hormone, which in nature is supposed to be an iodised albuminoid, possesses also an anti-toxic action such as is indicated below.

The pathogenesis of endemic goitre may be somewhat as follows:- The goitrogenous agent is introduced into the economy of the individual, either by the drinking water or by some other vehicle, and in the intestine produces toxins which are absorbed into the blood. (According to some investigators (127)^{*} the organisms themselves do not obtain access to the bowel of the individual, but produce the condition of goitre by means of their toxins which are consumed with the drinking water). (Microscopic and other methods have consistently failed to reveal the presence of organisms either in the blood or in the thyroid).

The power for harm of the specific cause has been shown to be short lived and, provided there is no further supply of this cause, nothing more transpires - the toxins in the circulation are neutralised by the thyroid secretion and the organisms which produced them either become inactive or die out. (If only the toxins are taken into the body naturally a continued supply from without must be kept up if the disease is to progress).

Assume however that the supply is kept up. There is then a constant pouring of toxins into the circulation calling for a steady increase of output of anti-toxine by/

* See also Bircher's view - p.66.

by the thyroid. The blood supply to the gland is increased concomitantly with the increase of activity of the secreting epithelium, and, provided the requirements of the individual are sufficiently met by these changes, there is no further development. Should this not be so however, there commences an increased hyperplasia producing that visible hypertrophy which constitutes a goitre. This tendency to hypertrophy is increased if, as has been stated (Oswald), the thyroid secretion is less active in this condition than in health.

With the increased formation of active glandular tissue there is also increase of the scaffolding i.e. the fibrous tissue. When this condition of hypertrophy dependent upon hyperactivity has continued for some time degenerative processes set in and give rise to the various secondary changes which characterise the different types of goitre.

The primary enlargement of the thyroid in endemic goitre seems to be therefore a defensive process on the part of the body and is analogous to the temporary enlargement sometimes met with in certain septic conditions, suppurations, etc., (v.p.96). It is the response of the thyroid to the call of the body for help in dealing with the toxins circulating in the blood.

SECTION VI.Course and Symptoms.Course:

As has already been indicated (p.84) the probability is that a large proportion of individuals living in an endemic goitre area exhibit the disease - that is, they have the causal agent in the system, the toxins in the blood, and the increased activity in the thyroid, though, in a greater or lesser proportion of these individuals according as the virulence of the endemic influence is low or high, the thyroid is capable of coping with the toxins proceeding from the causal agent in the bowel without visible hypertrophy, and the condition remains unrecognised.

Thus, had one the opportunity of examining microscopically many apparently healthy thyroids in a goitrous district, it is probable that one would find signs of increased functional activity, viz: increase in the size, granular structure, and number of the cells of the secreting epithelium of the vesicles, etc.

It is obvious that through paucity of material there must be insufficient direct evidence on this point as regards man, but that such changes occur in animals has been demonstrated by the work of Horsley, Marine, Lenhart, and others. Bircher too found that
a/

a considerable number of persons dying in the hospital at Aarau from causes distinct from goitre showed changes in the thyroid similar to those found in true goitre with enlargement.

The following notes on the course of the disease as artificially produced are extracted from the results of experiments conducted by McCarrison (66) upon himself and others in North India in 1906 and 1907:- The goitrogenous agent was administered continually as the filter residue of a notoriously goitre-producing water. In about thirteen to fifteen days the thyroid swelling made its appearance; after this it fluctuated from time to time, reached its maximum in about thirty days, and remained stationary. Some cases showed no enlargement, and others showed only increased pulsation in the blood-vessels of the neck.

When a previously healthy and susceptible person comes to reside in an endemic area and is exposed to the source of the infection, the thyroid enlargement generally appears after a somewhat longer lapse of time than the above, i.e.: from six to twelve weeks, though in some cases it may develop in so short a period even as eight to ten days (Bally) (v.p.43). At first, as is to be expected from the pathology of the condition, the goitre tends to be soft in consistence and uniform in enlargement, though sometimes one or other lobe (more usually the right) may be the more prominent.

With/

With this, there is often considerable pulsation in the neck vessels.

Here, as in the artificially produced disease, the enlargement is not steadily progressive, but tends to fluctuate and occasionally disappears altogether, either spontaneously or as the result possibly of very desultory treatment. Where it persists however, and the patient is subjected to goitrogenous influences for a prolonged period of time, the various secondary degenerative changes set in and typical large cystic and adenomatous goitres are the result.

As already stated, (v.p.36) conditions which tend to throw any additional strain upon the thyroid apparatus, as menstruation, pregnancy, etc., are inclined to indicate their presence in the goitrous individual by temporary increase in size of the tumour; this temporary increase is sometimes seen also in certain illnesses (v.p.96), Robinson (24) says "in any temporary illness" but my experience does not allow me to follow his quite so far.

In old age there is sometimes a tendency to shrinkage of the thyroid swelling though often it continues throughout life.

Various complications may occur from time to time in the course of the disease. These are discussed below under "Symptoms".

In some cases the enlarged gland may, from some cause/

cause or another, suddenly give rise to symptoms of acute hyperthyroidism, in fact many cases show ordinarily a slight degree of hyperthyroidism, though probably few reach the severity of symptoms exhibited by the following instance quoted from my casebook: Female, aet.58, native of Lochtayside. Has a large fibro-cystic goitre of right lobe and isthmus, with slight enlargement of left lobe. Condition first appeared about puberty and until recently never caused any symptoms further than of physical inconvenience from its size. Last autumn the patient broke down under the strain of nursing two old and very helpless aunts; symptoms of hyperthyroidism then appeared for the first time - marked tachycardia and arrhythmia, sleeplessness and nervousness. While she was in this condition her husband died very suddenly and unexpectedly; her symptoms immediately became exaggerated, the heart's action became very irregular, there was much dyspnoea, slight exophthalmos, insomnia and delirium, and great emaciation. Patient refused operation and died in nine months from exhaustion. (v. Case II. "Recorded Cases." Section X).

Seasonal fluctuations in the course of the disease, due certainly to intermittence in the supply of the goitrogenous agent, have already been referred to (v. pp.57-58).

Symptoms:

In simple endemic goitre there are generally no symptoms beyond a feeling of slight fulness in the neck and/

and any complaints the patient has to make are generally directed against the tumour on account of the deformity it produces. When the enlargement becomes excessive it draws increased attention upon itself on account of its unwieldiness, and on account of the sensations of dragging and constriction it may produce upon the throat.

As stated above, a few cases show ordinarily slight symptoms of hyperthyroidism. In the cases I have observed, this generally is evidenced by the abnormal restlessness and fidgetiness of the patient, and the excitability of the heart. These symptoms however are more the exception than the rule and cannot be taken as a "sine qua non" of ordinary endemic goitre; and the same may be said of the myxoedematous symptoms which occasionally arise in cases in which there has been fibrous contraction, producing obliteration of vesicles.

Of more importance are the secondary symptoms which frequently arise in the course of the disease from pressure of the tumour upon the surrounding parts. These pressure effects do not bear any proportion to the size of the goitre, but depend more upon the situation of the tumour and the effect of muscles and fasciae in binding it down, and upon the manner (i.e., whether it bulges externally or internally) and rapidity of its growth. They may be classed according to the nature of the structure pressed upon:-

a/

- a. Pressure upon the trachea.
- b. Pressure upon the recurrent laryngeal nerves.
- c. Pressure upon the cervical sympathetic and other nerves.
- d. Pressure upon the great bloodvessels of the neck.
- e. Pressure upon the oesophagus.

Pressure upon the Trachea:

Pressure upon the trachea may produce a varying degree of dyspnea. This symptom is commoner amongst men and children than amongst women, for in men the muscles and fasciae are generally more rigid, and in children the tracheal rings are softer than in women.

This pressure is most likely to be exerted by large tumours which embrace and constrict the trachea, the pressure being more often lateral than antero-posterior. Comparatively small growths may produce this symptom sometimes, particularly if they are quick growing, or if they are situated low down or behind the sternum.

Sometimes in place of constriction of the trachea there is displacement. Erichsen (51) mentions a case in which he found the larynx and trachea pushed completely over to the left, forming a long convexity in that direction, whilst the carotid sheath on the right was thrust behind the sterno-mastoid muscle.

Pressure upon the recurrent laryngeal nerves:

Pressure upon this nerve may occur, but dyspnoea is/

is less often due to this than to pressure on the trachea because the nerve is pushed aside and does not suffer the full effect of the pressure. Irritation of the nerve however may produce spasm of the glottis, and if pressure is continued, paralysis of the abductors of the vocal cords (crico-arytenoidei postici muscles) results on one of both sides according to the nerve pressed upon.

These nerves are more often involved in cases of malignant disease, than in true goitre. In fact their involvement leads one to suspect the presence of the former condition. In malignant disease the involvement is due to infiltration of the growth, and in goitre to pressure alone.

Pressure upon the Cervical Sympathetic and other nerves:

Pressure upon the Cervical Sympathetic is shown by contraction of the pupil on the affected side and ptosis.

Pressure upon the vagus has been believed to be the cause of the sudden death sometimes met with in large goitres.

Pressure upon the nerves of the brachial and cervical plexus is rare in goitre, and should lead one to suspect malignancy, if it occurs. It gives rise to referred pains.

Pressure upon the great bloodvessels of the neck:

Pressure/

Pressure upon the large veins of the neck may produce congestion of the head and neck, with giddiness, headache, tinnitus aurium, and confusion of thought.

Pressure upon the carotids have been known to produce cerebral symptoms - anemia, syncope, and even convulsions.

Pressure upon the Oesophagus:

The oesophagus generally escapes pressure from a goitre. When pressure effects do occur however they are usually caused by a left-sided swelling. There may be dysphagia and difficulty in swallowing solids.

SECTION VII.Objective Signs, Diagnosis, and Prognosis.Objective Signs, etc.:Clinical appearance of the thyroid enlargement.

In mild cases there is merely a slight fulness in the front of the neck, internal to the sterno-mastoid muscles; this may be over the whole gland or may be irregular, i.e.: either the gland as a whole, or one or other lobe, or the isthmus separately, may be affected.

The skin over the swelling is not discoloured, unless there is inflammation present. McKenzie (36) states that in most cases he has noticed a peculiar sallow or yellow tint in the skin of the face; probably this is identical with the "cachexia" described by Grasset (31). I have not observed this as a prevailing feature in the cases of endemic goitre in the Lochtayside area.

As the gland increases in size and becomes the seat of fibrotic and cystic degenerations its contour becomes more irregular and lobulated. Sometimes it forms a thickening of the neck, which extends from ear to ear, sometimes a pendulous mass which may attain to huge proportions/

proportions (Alibert records a case in which it reached to the middle of the thigh, and Fodere mentions another in which the gland weighed eight pounds).

Pulsation is sometimes visible in the enlargement; this may be due to the vascular nature of the tumour itself, or to the transmitted pulsation of the carotid artery behind, or to an enlarged thyroid vessel.

Palpation of the thyroid enlargement.

The swelling is usually freely movable and soft; it is firm in fibrous goitre, and may be hard if there are calcareous or cartilaginous changes present. In cystic goitre the cysts may be small and tense and are then indistinguishable from small adenomata; in some cases however a cyst may be large and lax and show fluctuation.

Pulsation may be felt - which is distensile, eccentric, and synchronous with the cardiac systole.

A sign which is sometimes said to be pathognomonic of thyroid tumours, and which depends on the anatomical relationship of the larynx and the gland to the cervical fascia is observed when the patient goes through the act of swallowing:- the swelling rises and falls with the upward and downward motion of the larynx and trachea. In the vast majority of cases a swelling in the position of the thyroid gland which exhibits this sign is the outward indication of an enlargement of that gland. There are certain fallacies however attached to this test/

test which have to be kept in view, viz:-

- A. There are some thyroid tumours which do not give it:-
- a. where the tumour is very large.
 - b. where the tumour is fixed by inflammatory adhesions.
 - c. in malignant disease where there is infiltration of the surrounding tissue.
- B. There are some tumours not of the thyroid gland in which this sign is observed. These have to be differentiated by their position, etc.:-
- a. Cyst from the thyro-glossal duct. Typically this is situated too high in the neck to offer any real difficulty to correct diagnosis.
 - b. Enlarged lymphatic glands may adhere to larynx and trachea and simulate thyroid enlargement (here the history is a guide to diagnosis.)
 - c. Suppurative or syphilitic perichondritis of the thyroid cartilage.
 - d. A swelling not thyroid in origin, but lying in front of it, as a sub-hyoid bursa or a sebaceous cyst.

Diagnosis:

As a rule there is not much difficulty about the diagnosis of endemic goitre, though other forms of thyroid enlargement which may occur as well in an endemic area as elsewhere, must be neither overlooked nor confused.

The/

The differential diagnosis of the various types of endemic goitre has been described above under the headings "clinical appearance" and "palpation", as has also that of several distinct conditions which under certain circumstances may simulate goitre.

There still remain to be considered however several conditions:-

- a. "Inflammatory" enlargement of the thyroid gland.
- b. Malignant disease (carcinoma, sarcoma, papilloma).
- c. Aneurism of the carotid artery, or of thyroid arteries.
- d. Tracheocele (aerial tumour).
- e. Hydatid Cysts of the thyroid gland.
- f. Tuberculous disease)
- g. Gummatous disease) both rare.
- h. Enlargement from acute or chronic pyogenic infection.
- i. Multiple abscesses in thyroid in pyemia.
- j. Exophthalmic goitre (Parry's, Grave's, or von Basedow's disease)
- k. Chagas' parasitic thyroiditis.
- l. Lymphadenoma.

A few notes on the chief of these must suffice:-

Inflammatory enlargement.

1. Primary thyroiditis - rare.

The usual signs of inflammation - pain, fever, etc.
- indicate the nature.

2. Metastatic thyroiditis - rare.

This /

This most commonly occurs during the course of parotitis. Here also the history and signs distinguish the condition.

3. Thyroid enlargement is occasionally met with in cases of:- Acute rheumatism, malaria, enteric fever, smallpox, cholera, Secondary syphilis, influenza. It subsides as the primary disease abates.

Malignant disease of the thyroid.

In early pre-infiltration stages this is very difficult to distinguish from adenomatous goitre. Usually there are lancinating pains. The hardness of the tumour and the age of the patient are also guides to diagnosis.

Later, the condition of the patient, the fixation of the tumour, and involvement of glands, nerves, etc., are conclusive.

Carotid Aneurism simulating a pulsating goitre.

The aneurism does not move with the trachea on deglutition. A goitre is more usually fixed towards the middle line, whereas a carotid aneurism is more firmly fixed under the sterno-mastoid. A goitre too is more or less separable from the artery, when the pulsation ceases.

Aneurism of the thyroid arteries:

These are usually known by their site and pulsation, and/

and by their diminution or disappearance under pressure.

Tracheocele (88)

This very rare condition is due to escape of air into surrounding tissues from the trachea. It changes in volume, i.e., increases with expiration, cough, etc., diminishes with deep inspiration and forced extension of the head, and disappears on compression.

Exophthalmic Goitre.

This condition presents a clinical picture of its own sufficient to identify it, viz:- exophthalmos, heart symptoms, nervous symptoms, etc. As already shown (v.p.88) an ordinary case of endemic goitre may develop all the symptoms of exophthalmic goitre.

Parasitic thyroiditis.

This disease in its acute stage also presents a clinical picture of its own (v. p. 65). In later stages the condition cannot be distinguished from ordinary endemic goitre. The age of onset may be a guide.

Lymphadenoma.

The History, the general condition of the patient, the enlargement of the spleen which usually occurs, and the occurrence of rigors and intermittent pyrexia should be sufficient to distinguish this condition.

In addition to the various facts, etc., quoted above/

above as of service in separating doubtful cases the evidence afforded by an examination of the blood (v. p. 81) is always available and should be utilised .

Prognosis.

Prognosis is good. As a rule the thyroid condition in endemic goitre occasions the sufferer little or no inconvenience beyond that directly dependent upon the size and weight of the tumour. In some cases the enlargement of the gland has been known to disappear spontaneously without interference, but where it persists it is generally more or less amenable to appropriate treatment.

The risks of the condition have already been indicated but may here be summarised:-

- a. As the result of pressure on surrounding objects, symptoms of varying nature may be produced (v. p.89), of these pressure on the trachea being commonest is most likely to give rise to alarming symptoms, and when it does so, always calls for surgical interference.
- b. The growth may become malignant. This is not a common occurrence.
- c. The enlarged gland may from some cause or another become overactive, with consequent supervention of symptoms and effects of hyperthyroidism (v.p.87-88).
- d. Hemorrhage from rupture of a bloodvessel on the wall of a cyst or in the body of a large soft goitre may/

may occur, sometimes with serious consequences (Osler records a death from this accident).

- e. Sudden death has been known to occur in patients with large goitres. The cause of this is difficult to determine, but has been thought to be associated with pressure on the Vagi.

SECTION VIII.Treatment.

Hand in hand with the deepening of our insight into the nature of endemic goitre our methods of treatment are evolving, and passing from the unsatisfactory regions of empiricism to the domain of rational medicine - the true abode of all scientific treatment.

Of the numerous older methods of combating the disease, many were attended with considerable risk and are now of interest more from an historical than a practical standpoint. A few however - notably the Iodine treatment - are still to be found in the modern medical anti-goitre armamentarium, but are now used rationally and in selected cases where they were previously employed empirically and at large.

With endemic goitre as with all other diseases of an infective nature the question of treatment resolves itself naturally into two parts:-

- I. Preventive: the treatment of the endemic - directed towards the stamping out of the disease from the community.
- II. Curative and palliative: the treatment of the affected individual.

Preventive Treatment:

From the nature of the etiology of the condition the route along which preventive treatment must pass is/

is clearly indicated.

The water supply of the affected area must be overhauled and brought into line with modern hygienic requirements. If this supply is derived from a doubtful source it must be discarded in favour of a better, and if such be not available, proper means must be taken to protect the existing one from all sources of contamination. Failing this, all water must be thoroughly filtered or boiled before being used for human consumption.

In many country districts, well-exemplified by the Loch Tay Area, the water is drawn either direct from some unprotected burn, or from some storage tank supplied from a burn or a spring. In the latter case as often as not (or more probably oftener than not) this tank is cleaned but rarely and then in a most cursory manner. The remedy is obvious.

As water has been shown to be not the only vehicle of the infection preventive treatment must not be taken to begin and end with the perfecting of the water supply. In particular, must residents in goitrous areas, more especially those whose employment brings them into contact with the soil, pay careful attention to the thorough cleansing of the hands before partaking of food. In addition too in these districts, should the practice of eating uncooked vegetables be condemned, and proper care of carious teeth coupled with the regular/

ular application of the tooth brush be observed.

The habits of the people must be got at; an elementary knowledge of Hygiene must be instilled in the public mind, and this will only be possible when Hygiene is compulsorily taught in the board schools. The doctor on his rounds has no time to lecture to his patients on this highly important matter; nor does the duty lie with him, it is a national concern and should be attended to by the State.

When the poorer and labouring classes understand and appreciate to the full the evils of overcrowding, deficient ventilation, etc., and the benefits of fresh air and cleanliness, then and then only can the millennium of Public Health be in sight and infectious and other diseases - endemic goitre among the rest - cease to be a curse in the land.

Treatment of the Affected Individual:

The treatment of the affected individual falls for description under five heads, viz:-

- a. General measures,
- b. The internal and external application of drugs, etc.,
- c. The use of vaccines, etc.,
- d. Electrical treatment of the thyroid tumour,
- e. Surgical methods of dealing with the thyroid tumour.

a. General Measures;

The general measures indicated in the treatment of
a/

a case of endemic goitre are similar to those described above as "Preventive", and are directed against further ingestion of the specific cause of the disease and towards the building up of the health of the individual thus to render him (or her) more fit to contend with the condition should this cause continue to be exhibited.

The former of these two ends may be achieved by sending the patient away from the endemic area for a time. Hyperactivity of the thyroid is then no longer called for and the gland subsides. If the disease is in an early stage there is generally complete disappearance of the enlargement; should the condition be of older standing however, with more permanent fibrotic and cystic changes, the tumour does not entirely disappear, but the disease is often arrested. As there seems to be no immunity developed against the disease, the patient whose goitre has been cured by residence without the goitre area is liable to a recurrence on his (or her) return to it.

Should this means of treatment be impracticable (as it generally is) a theoretically equal result should be obtained by close observance of the preventive measures already laid down, viz:-, no water should be consumed which has not previously been thoroughly filtered or boiled, raw vegetables should not be eaten, care in cleansing/

cleansing the hands before meals and proper care of the teeth, etc. should be observed.

Improvement of the general surroundings should be aimed at, and this, coupled with good nourishing food, does much to enable the defensive mechanism of the patient's system to grapple with the disorder.

b. The internal and external application of Drugs.

Before entering upon a discussion of this subject it is instructive to glance over a list of some of the remedies (now mainly discarded) at one time or another advocated as of service in dealing with endemic goitre:-

Internal Applications.	Intraglandular injections of:-
Various mercury preparations	Iodine
Digitalis and Camphor (Ossiander)	Tinctura Ferri Perchloridi
Sulphuret of Potash	
Muriate of Baryta (Postiglione)	<u>External Applications.</u>
Cicuta or Belladonna	Stimulating lotions
Muriate of lime	Astringent lotions
Preparations of potash and Soda	Cold bathing and douches
Strychnine (Murney)	Mercurial applications
Ammoniated Muriate of iron	Cicuta and ammoniacum plasters
Mineral, sea, and dis- tilled waters	Friction with or without liniments.
Burnt Sponge	Iodine as liniment
Ashes/	

Ashes of Fucus Vesiculosus (Russell)	Iodine as ointment
Iodine	Ointments of lead iodide
Iodides of Potash Ammonium and iron	" potassium iodide
Bromide of Potash	" biniodide of mercury
Iron and quinine	
Iron and aloes	
Fluoric acid, etc., etc.	

A consideration of the above list shows that, prior to the introduction of iodine as a therapeutic agent, of the various remedies, etc. practically not one has survived to prove its value. Although our present-day knowledge of the functions of the thyroid gland and of the exact etiology of endemic goitre is still far from perfect, it is sufficiently advanced to enable us not only to see how much of this older treatment was mere groping in the dark and of little avail, but also to explain in a rational manner the action of these remedies which, although employed empirically, were definitely found to be of good service. Thus, the use of distilled water is beneficial in cases traceable to an infected water supply in that while its administration is continued the goitriiferous water of the district is not used, and it is probable that any value the water of mineral springs may be found to possess is similarly to be explained. Again, sea-water no doubt owes/

owes such virtue as it may have to the traces of iodine it usually contains.

The story of the introduction of iodine in the treatment of goitre is of interest and will bear repetition here:- For a number of years burnt sponge and the ashes of *Fucus Vesiculosus* had been administered empirically, but often with marked benefit in cases of endemic goitre. Then came the discovery of Iodine, and, soon after, the second discovery by Straub of Berne, that this substance existed in these ashes. In 1820 he recommended its trial in cases of goitre. Coindet of Geneva, with whose name its first use is usually associated, proved its value and since then, for over three quarters of a century, it has proved a powerful ally in the struggle against the disease.

The kernel of the theory underlying the treatment with iodine lies in the fact that upon a constant supply of this substance the thyroid gland appears largely to depend for its efficient activity. In endemic goitre the thyroid gland has hypertrophied to meet an increased demand for its secretion; this secretion in parenchymatous, fibrous, etc., goitre is deficient in iodine (v. p. 81). Exhibit iodine. The gland receives a powerful physiological stimulus; its efficiency increases so that it is enabled to meet the increased demand without hypertrophy and the natural result follows, there is diminution or disappearance of the goitre.*
Particularly/

* For further explanation of the beneficial action of Iodine see below. "Intestinal Antiseptics".

Particularly is this so in cases treated early before permanent changes have taken place in the gland.

With the coming of the knowledge that the hypertrophy of the gland is a purely defensive process, the result of inimical processes occurring elsewhere, and not a primary and objectionable proceeding on the part of the gland itself, the thyroid is now looked upon as a zealous servant of the host and as such deserving of assistance rather than of suppression and discredit as an insubordinate.

How iodine acts in affording such assistance has been indicated. Recently another substance has been brought forward in the same cause - to wit, thyroid extract. This preparation has now passed its trial stage and taken its place in the front rank of anti-goitre remedies. The rationale of its action is very similar to that of the action of iodine, viz:- that of a supplement, stimulant, and adjuvant to the gland.

Thus it is seen that the rational treatment of endemic goitre by drugs which act by reinforcing the action of the thyroid is at present limited to the use of two substances, i.e., Iodine in its various forms and Thyroid Extract; and it is clear that only in early cases can one hope for total disappearance of the thyroid tumour. From what has been stated it is obvious also that in those few cases in which the increased activity of the thyroid has overshot the mark, and even slight/

slight symptoms of hyperthyroidism are present, treatment by these preparations is contra-indicated.

Methods of applying the Iodine Preparations.

External:- Iodine may be applied externally either as a paint of the tincture or of the liniment, or as an inunction of the Unguentum Iodi; or it may be employed combined with Potassium Iodide according to the following formula:-

R	Unguent. Iodi	1 part.
	Unguent. Potassii Iodidi	2 parts.

Possibly the best results however are obtained by inunction of the Unguentum Hydrargyri Iodidi Rubri (B.P.) The value of this process is said to be enhanced if the neck of the patient be exposed to the rays of the sun for some time after each application. This method has been widely employed in India and has been associated with the names of Holmes (89)(47), Cunningham (90), and Mouat (52). It has been suggested that the benefit which ensues is due to a greater permeability of a skin previously treated with iodine to the heat and other rays of the sun, and if this be the case herein may lie the explanation of the greater success which appears to have attended the application of the method in India than in this country. The usual method of applying this ointment (Ung. Hydrarg. Iodid. Rub.) in Britain is as follows: Every night or every second night for some/

some weeks (care being taken to avoid blistering of the neck to too great an extent by over free application) the ointment in small amount is applied to the swelling. The pharmacopocial preparation (16 grains to the ounce) is sometimes too strong and then may be replaced by another of 5 or 10 grains to the ounce with advantage. This treatment is best when combined with:-

The Internal Application of Iodine:-

Internally iodine may be given either as

R Tincturae Iodi m v, or

R Potassii Iodidi gr v - x, or

R Iodoformi gr ss - gr $\frac{ij}{i}$ (in pill),

Sig. Three times a day in gradually increasing doses.

The treatment must be extended over many weeks, with remissions at occasional intervals, especially should unpleasant symptoms supervene.

(Proceeding from the chemical and physical family relationship between iodine and fluorine Woakes(92) was led to experiment with fluoric acid in the treatment of endemic goitre and claimed a high percentage of successes in the cases in which he used it.

He recommended that m x of the 0.5% solution of redistilled Fluoric acid be given in $\frac{3}{i}$ water twice daily, and that the dose be gradually increased.

Ammonium Fluoride likewise has had its advocates. It has been given as a 0.75% solution in doses of m v - xx).

Administration/

Administration of Preparations of Thyroid Gland:

Thyroidal secretion contains iodine in an organic combination known as Iodothyrim (Thyroidin (Baumann)), but as the amount of Iodine used alone in treatment greatly exceeds the amount of iodine present in sufficient Iodothyrim to produce the same results it is obvious that the latter must act as the specific substance of the gland and not merely as an iodine compound(93).

Thyroid extract may be administered either as Thyroideum Siccum (B.P.) or in one of its many other forms. Small doses have been found more efficacious at the commencement of treatment than large, and it is now usual to begin with gr $\frac{\cdot}{1}$ or gr $\frac{\cdot\cdot}{1j}$ of the Thyroid. Sicc. each night. If found necessary the dose may be increased to gr $\frac{\cdot\cdot\cdot}{11j}$ once, twice, or even three times daily. This may be continued for six to eight weeks; if no improvement is manifest than the treatment may be discontinued as unavailing; should improvement have set in however it may be continued for some time longer (Murray).

If the pulse is accelerated under the influence of the thyroid extract, more than fifteen or twenty beats per minute a remission in the treatment is indicated (Murray). Cases which benefit under this treatment sometimes relapse when it is discontinued.

Drugs which act as Intestinal Antiseptics:

The discovery that intestinal antiseptics exert a curative/

curative effect on goitre was a confirmatory link in the chain of evidence which led to the tentative conclusion that the intestine is the habitat of the goitre producing agent in man, and this in turn naturally led to the employment of drugs of this class in the treatment of the affection.

Here, upon the "Intestinal habitat" assumption, we are able to give a further rational explanation of the beneficial effect of iodine. Its germicidal power is great; Ratimoff (94) places it third on the list of germicides arranged according to potency (mercuric chloride, silver nitrate, iodine). Its administration has already been described.

Fourth on Ratimoff's potency list of germicides comes Thymol, the action of which in endemic goitre was referred to in connection with "Etiology" (v. p.68). McCarrison, who has experimented largely with this drug, advises its use in much greater than pharmacopoeial doses and the following is the method of administration which he has found most efficient (67):- gr x of the drug, in coarse powder form, washed down with a draught of water, are administered morning and evening, the continuance of the treatment depending on the patient's reaction to it. While thymol is being given in such heroic doses it is important to regulate the action of the bowels, and also to see that the patients dietary contains no solvent of the drug.* Should this latter precaution be omitted most unpleasant symptoms of thymol/

* v. Appendix C. Table of Thymol Solubilities.

thymol poisoning are liable to supervene.

Other intestinal antiseptics which have been found of practical value are B naphthol and salol.

Here, as with other medicinal treatment one cannot expect disappearance of the thyroid tumour once permanent changes have taken place in the gland, and here likewise the more recent the case the more beneficial the treatment.

Other Drugs Sometimes Employed:

Where anemia accompanies the goitre the exhibition of iron is indicated, a useful combination being with arsenic.

Even where anemia is not present, arsenic has sometimes proved beneficial. It is best given as liquor Arsenicalis (m $\frac{\text{iii}}{\text{iii}}$ - $\frac{\text{iv}}{\text{iv}}$ three times daily - gradually increased).

In cases of simple parenchymatous goitre laxatives are of service, and should be freely administered as required.

c. Vaccines, etc. in the Treatment of Endemic Goitre:

In the Section on Etiology reference is made to the use of vaccines in treatment of goitre, and, as there indicated, these vaccines may be either autogenous or non-autogenous (v.p.66). The following account is epitomised from McCarrison's(61) report on the preparation and use of these vaccines:-

Autogenous/

Autogenous Vaccines.

- A. Composite vaccines prepared from organisms (from patient's intestine) which grow on Musgrave's agar medium** for the cultivation of amoebae.

When cultivating the amoebae from the intestines of goitre patients McCarrison was struck by the constant character of the bacillary growth which appeared on the above medium.

Inoculations of a composite vaccine prepared from these bacillary growths were found to produce complete disappearance of the thyroid swelling in cases in which no degenerative changes had taken place.

The vaccine was administered in doses of from 150 million to 350 million; inoculations were made at intervals of from seven to ten days; some cases showed complete cure after two inoculations, others had up to seven.

- B. Vaccine prepared from autogenous strain of Bacillus Coli:-

This vaccine was also administered in doses of from 150 to 350 million, at intervals of from two to ten days. Under these inoculations the same disappearance of the thyroid tumour was observed as under those of the composite vaccine.

- C. Vaccine prepared from spore bearing organism which has been isolated from the faeces of goitrous patients:-

The/

** An alkaline and feebly nitrogenous medium.

The case on which McCarrison based his findings in this instance was not treated with an autogenous vaccine, but with a vaccine of a spore bearing organism. isolated from the faeces of a goitreous pony. Here also the thyroid tumour disappeared.

Non Autogenous Vaccines:

A. Staphylococcus vaccine - prepared from a case of caries of bone - was found to produce results equally striking. This was partly to be expected as staphylococci are normal inhabitants of the human intestine.

The vaccine treatment of goitre, as shown by these statements, gives promise of proving of considerable service in dealing with individual cases, one advantage it possesses over the treatment by drugs being its shorter duration. It is still however mainly in the experimental stage, and time and further investigation are required to show its full practical value.

Lactic Acid Bacillus in the Treatment of Endemic Goitre:

The following method of treatment though included in this sub-section might more fitly have been bracketed with the treatment by intestinal antiseptics, for it is essentially a process depending on bowel sterilisation, at all events as regards noxious organisms. It is Metchnikoff's "Soured Milk" treatment and, like the above, has been experimented with and described by McCarrison. In the cases in which he employed it, fresh cultures of the Bacillus Bulgaricus were used, some of the/

the patients receiving 12-20 oz. of soured milk daily before the first meal of the day, and others 10 oz. morning and evening. The eight cases experimented upon were all of several months standing, and of the eight, four were cured, two improved, while two showed no change in six weeks.

d. Electrical Treatment of the Thyroid Tumour:

Electricity is not much used in the treatment of endemic goitre, though at one time or another, and in one form or another, it has been tried and has found its advocates.

Galvanism.

Dowse(95) (v. below) reports favourably on the combined application of galvanism and massage. He recommends the following procedure:- "Bring from six to ten (gradually increasing the strength every third day) Leclanché cells into action; place the positive pole (a flat electrode) over the back of the neck, and the negative pole (a large sponge) over the gland, let the current pass directly and continuously for ten minutes; then quickly alternate, giving about twenty shocks" (v. below "Massage").

Electrolysis.

Electrolysis is not now employed as a usual method in the treatment of endemic goitre, although at one time several favourable results were reported from the application of the process(96). Duncan used a current of from 40 to 80 milliamperes and both electrodes were introduced./

introduced. De Costa (7) recommends that only the negative electrode be pushed into the gland, the positive being applied to the surface. The chief difficulties were found to lie in the manipulation of the needles, and in the possibilities of doing harm to important structures.

Ionic Medication:

I am not aware that ionic medication has been applied in the treatment of Endemic Goitre but, from the nature of the process, I should imagine that the introduction of certain of the iodine preparations by this method might be attended with benefit in early cases of the disease.

e. Surgery in the Treatment of Endemic Goitre.

Under this head I propose to give a brief account of the treatment of goitre by methods generally understood as surgical in the strict sense of the term, and also by one or two other procedures of a non-medical nature. These methods will be considered under the following sub-heads:-

1. External:- counter-irritation and massage.
2. Injections, use of setons, artificially produced suppuration, tapping.
3. Ligature of arteries.
4. Operations on the thyroid body.

Counter-irritation.

According to Berry (97) counter-irritation is not likely/

likely to be productive of much benefit unless carried to the extent of blistering of the skin. This method is less practised now than formerly, having been mainly supplanted by the external application of the various compounds of iodine.

Massage.

The combined application of massage and galvanism has already been referred to, the form of massage which has been found most useful being "Vibratory Petrissage", the manipulations of the neck at each séance following an application of the galvanic current. The treatment is employed thrice weekly for some months (95).

The massage probably acts by inducing an improvement in the blood supply of the gland and by assisting, by physical expression, in the passage through the inter-cellular channels of Hürthle of the contents of the glandular vesicles and thus, by introducing a greater amount of the anti-toxic secretion to the lymphatic system and thence to the bloodstream, brings to bear upon the toxic products of the organism at the root of the trouble a greater amount of this secretion. Probably too it encourages the gland to increased activity, through stimulation of the sympathetic ganglia of the neck - this last act being enhanced by the simultaneous employment of the galvanic current.

Injections:

Injections into the body of the thyroid gland in
the/

the treatment of endemic goitre have generally been either of iodine (Tincture) or of perchloride of iron (tincture). As the latter is injected with a view to setting up suppuration it is referred to below; it is the former alone which falls to be discussed here.

It was thought that the direct introduction of iodine into the substance of the gland would be more efficient than the other modes of administration but the method - which consists in the injection of m XX - XXX of Tinctura Iodi into a parenchymatous or fibrous goitre every third day, or of m XV of a 40% solution of iodine in oil (98) once a week - though still advocated and practised by some surgeons (Sir Felix Semon, Dubar) is by most viewed with disfavour; suppuration and death have ensued far too frequently to make this treatment popular.

Horsley by experiment has shown that death in such cases is due to the iodine passing from the syringe directly into a large bloodvessel, an accident which from the vascular nature of the tumour it is difficult to avoid.

The use of Setons:

Cures following upon the use of setons have been recorded (99). The risks however accompanying the inflammation and suppuration set up by the process, apart from the dangers attendant on the passing of a sharp instrument blindly into so vascular an organ as the thyroid, are sufficient to condemn it.

Artificially/

Artificially produced suppuration:

This was found to produce contraction and in some cases complete disappearance of the goitre, and has been brought about in various ways - as by the use of setons (v. above), and by injections of an aqueous solution of the perchloride of iron ($\frac{1}{1}$ - $\frac{1}{1}$) of a solution $\frac{1}{1}$ to the $\frac{1}{1}$). This latter method which is described in very full detail by Morell McKenzie (100) and Hovell (102) need not be more than merely mentioned here, as it is no longer practised, the dangers attendant upon it being considerable.

Tapping.

Tapping was at one time popular as a means of dealing with cystic goitres and was done with trocar and cannula. It was recommended (101) that large cysts should not be emptied all at once, but should have the process repeated several times. Even with this precaution however recurrent hemorrhage, which sometimes proved fatal, either from its extent or from pressure of the rapidly enlarging swelling upon surrounding structures, was found liable to occur and the method has fallen into deserved disrepute.

In earlier days, tapping was generally the prelude to intraglandular injection of perchloride of iron or of iodine (7).

Ligature of Arteries:

This somewhat uncertain method of dealing with parenchymatous goitre has recently been revived.

The/

The ligature of the superior thyroid arteries alone as originally recommended by Wölfler and first executed by Blizard(103) is not a difficult operation, but as the blood supply of the gland is so extensive that merely to ligature one or two of the main vessels cannot be conceived to have any permanent beneficial effect it would appear to be necessary to proceed further and ligature also the inferior thyroid arteries, and as these are deeply situated behind the gland the operation becomes at once a severe and difficult procedure, the large veins being particularly liable to injury.

Kocher (104) advises ligature of two or more of the thyroid vessels in preference to excision in cases of large vascular colloid tumours where the risk of hemorrhage is great. He also speaks well of the method as a preliminary measure to excision, as it improves both the local and general conditions by causing diminution in the size of the tumour and shrinkage of the vessels.

Operations upon the Thyroid Body.

Kocher, whose experience in the surgery of the thyroid is greater than that of any other surgeon, describes various operations for the treatment of goitre:-

Excision.

Enucleation.

Resection.

Enucleation-/
/

Enucleation-resection and Enucleation-excision.

Evacuation or Exenteration.

Operation for intrathoracic goitre.

Operation for recurring goitre.

The nature and applications of these will be merely indicated here; a full account is given in his "Operative Surgery" (105). He has operated now on several thousands of cases with a death-rate, in his latter series, of practically nil. He therefore does not hesitate to recommend operation when he considers it called for - as he does in the following conditions of the disease:-

1. Whenever there is respiratory embarrassment.
2. Whenever the tumour shows a tendency to become inflamed.
3. Whenever the tumour shows a tendency to become malignant.
4. When the goitre is "deep" i.e. growing downwards towards the inlet of the thorax.
5. When signs of hyperthyroidism threaten or supervene.

Excision: is the operation most generally applicable, particularly in diffuse cases; the others listed above are indicated only in special cases (v. below).

Enucleation: is generally performed in cases where there are numerous well-defined colloid nodules large and small scattered equally through both halves of the gland. Although this operation is easier to perform than excision/

cision, and is good in that it leaves healthy gland tissue behind, the risk of hemorrhage, which is particularly liable to recur, is much greater. Kocher therefore recommends its use only:-

1. where the goitre is very adherent to the capsule from old inflammation.
2. if the other half of the gland is atrophied or has previously been removed.
3. where there are one or two nodules in otherwise healthy gland tissue.
4. if there is a single nodule present which has produced pressure atrophy on surrounding tissue, and therefore lessened the risk of hemorrhage.

Resection: (i.e., resection of the diseased part of the gland, as suggested by Miculicz) is done only in exceptional cases as there is great risk of hemorrhage and the stumps of tissue are very liable to necrose. It is indicated only:-

1. where the nodules are small and prominent and can be easily separated from the substance of the gland to a certain extent and isolated.
2. in diffuse colloid degeneration without formation of definite nodules where the firm mass presses upon both sides of the trachea and is difficult to lift out.

Enucleation-resection and Enucleation-excision: is a combination method in which the anterior easily accessible/

ible portion of the growth is excised, and the posterior part is enucleated by resection, the posterior part of the inner capsule of the gland being left behind.

This method is not recommended in diffuse colloid degeneration in the form of very small follicular colloid foci, but is only advisable where there are large colloid or cystic masses forming spherical tumours imbedded in relatively healthy gland tissue.

Evacuation or Exenteration: This operation consists in dividing the capsule of the goitre and scraping out and expressing the colloid contents, the walls of the cyst being left behind. It is the simplest method of all and is useful:-

1. in dealing with nodules of large sizes whose contents are breaking down and softening, and which are adherent to the surrounding parts.
2. in multiple small softened tumours which can be sufficiently pulled forward to be cut into and evacuated, and where the relatively small amount of hemorrhage can be controlled by ligature or suture.
3. where there is danger of asphyxia and where the pressure on the trachea must be quickly relieved during the operation, (indicated here on account of the rapidity with which it can be done).

Operation for Intrathoracic Goitre: this is a very difficult operation and requires both skill and experience. The various methods already referred to are applied/

applied as the surgeon finds necessary.

Operation for Recurrent Goitre (Struma Recidiva):

Brunner has shown that of the 18% of recurrence after thyroid operations the majority are after enucleations - the reasons for which are obvious. In these recurrent cases, if there is any dyspnoea, the operation is likely to be difficult, because of the large size or because of the deep extension of the growth, and this quite apart from the cicatrices of the earlier operation which cause adhesion to the surrounding parts. The operation generally found to be most suitable in these cases is resection.

Additional Remarks on the Operative Treatment of Endemic Goitre.

1. In cases of simple parenchymatous goitre with dyspnoea temporary relief often follows mere division of the isthmus. As the dyspnoea is generally the result of lateral pressure from the lobes, this relief is ascribed to partial depletion of the lobes by drainage from the cut surfaces. However this may be, cases are on record in which more permanent benefit has followed this procedure. Stokes(106) has recorded a case in which the lateral enlargements sensibly diminished after section and ligature of the isthmus, and I have notes of a case (v. p.137, Case 5) of a woman in this district who had her isthmus divided many years ago for the relief of dyspnoea, the operation being followed by/

by a gradual disappearance of the thyroid tumour.

2. It is undesirable to remove the whole of the thyroid on account of the liability thus produced to the onset of myxoedema. Although it is generally sufficient to leave even a small piece of the gland myxoedema has sometimes followed the removal of one lobe only.

Obviously the condition is commoner after excision than after any of the other operations described above.

3. The question of the anaesthetic is an important one in operations upon the thyroid, particularly when these are undertaken for the relief of dyspnoea. On account of the risks attendant on the use of chloroform and ether in these cases many surgeons prefer local to general anaesthesia. Local anaesthesia has the additional advantage in that the surgeon, by getting the patient to speak, is able to learn whether or not he is in dangerous proximity to the recurrent laryngeal nerve.

4. Tracheotomy in cases of Endemic Goitre: this is rarely called for as the proper treatment of a goitre producing dyspnoea is excision or enucleation. If however this should be found impracticable, tracheotomy may have to be resorted to, and the high operation performed if possible. The ordinary tracheotomy tube is not long enough to reach sufficiently low to relieve the dyspnoea, and a special tube must be used. A case of endemic goitre is one record(107) in which a labourer had/

had pursued his ordinary vocation for five years with a four inch tracheotomy tube through his thyroid in his trachea.

5. Acute Tetany may set in after Thyroid Excision: and, unlike myxoedema, does not yield to thyroid medication. It is now believed that this condition is produced by the concurrent removal of the Para-thyroids which lie, two on each side, in close relationship to the lateral lobes of the thyroid (in some animals they are imbedded in the thyroid).

Vogt(108) reports a case of "Tetania Strumipriva" in which the general condition temporarily improved under parathyroid tablets; Beebe(111) has used in these cases hypodermic injection of nucleo-proteid principle of para-thyroid, and Kocher(111) has attempted transplantation of parathyroids of animals into muscle or into bone-marrow.

6. Tenotomy of the Sternomastoid muscles and of the Cervical Fascia has sometimes been done for the relief of dyspnoea.

SECTION IX.Additional Remarks; Summary and Conclusions.Additional Remarks:-

The association between Endemic Goitre and Endemic Cretinism as regards distribution is well known and the cause in both diseases is probably the same, though the manner in which one agent which in certain individuals can lead to hypertrophy and occasionally to hyperactivity of the thyroid can in others lead to congenital deficiency of the thyroid secretion (congenital myxoedema), either from hindering the ante-natal development of the gland or from producing some morbid change which interferes with its function, is not understood.*

In all probability the question of dosage plays an important part - thus, though endemic cretinism never occurs apart from endemic goitre, it only occurs in regions of very high goitrous endemicity, e.g., Switzerland, certain parts of France, India, etc., whereas in regions of lower goitrous endemicity it is rare or absent e.g., Great Britain.

Another frequently associated condition of extreme interest but concerning the exact etiology of which even less is known is Congenital Deafmutism.

In the Loch Tay Endemic Goitre Area, cretinism is unknown/

* Bircher's theory on this matter has already been mentioned (p.66).

unknown and of deaf-mutism I have been able to discover only two cases - sisters, resident in Acharn, both goitrous, one of normal appearance, the other stunted and of a semi-cretinoid appearance though, according to her friends, of normal intelligence.

Summary and Conclusions.

In drawing deductions from observations on any endemic of limited extent and of a minor degree of intensity one is apt to fall into the error of forming generalisations from insufficient data, not merely when these deductions bear upon the endemic as a whole but also, though in a lesser degree, when they deal with individual cases grouped and considered collectively.

I shall therefore base my concluding remarks on the subject of Endemic Goitre mainly upon the critical study of the facts and arguments derived from the literature, etc. on the condition as already set forth.

Certain views and conclusions on various points have already been summarised at the ends of several of the sections and I shall content myself here with a brief, final, collective survey in view of the evidence of the Thesis as a whole.

That endemic goitre is a chronic infective disease requiring continued administration of the specific cause seems highly probable, though there is as yet no entirely satisfactory proof of this, nor has it been definitely/

definitely shown that the condition is produced by a living agent. Therefore in the meantime all that can be said of McCarrison's definition (v.p.1) of endemic goitre as "an infectious disease in which the seat of the infection is the intestinal tract, etc", is that it is indicated but not proved by the evidence before us.

Circumstantial evidence however has been seen to point strongly to the following conclusions:-

- A. The disease is probably due to an organic cause which, in view of the lymphocytosis and eosinophilia, may be protozoal in nature.
- B. The endemic character of the disease points to the soil as the first habitat of the goitrogenous agent, and water would appear to be the chief vehicle by which it or its products obtain access to the affected individual.
- C. Allowing that the disease is probably organic in origin, it is not clear whether the causal organism itself actually obtains access to the body of the host, or only produces its effects from without, by means of toxins conveyed in the drinking water, etc. That cases have been recorded in which contagion appears to have played the chief part would seem to indicate however that the organism and not the toxin alone is the actual cause.
- D. That the intestine is the seat of the infection in man/

man is not proved. The evidence (pp.67-68) is suggestive but not conclusive.

E. Continued administration of the poison is necessary to produce and maintain the disease. This admits of one or other of the following explanations:-

1. The condition is the result of ingested toxins produced by some agency outside the body.
2. The organism itself obtains access - probably to the bowel - but is unable to survive there for more than a short period.

F. The presence of lime or magnesia in the soil is favourable but not essential to the occurrence of the disease. Three suggestions are offered in explanation of this:-

1. Such a soil is more porous and therefore more likely to retain organic pollution.
2. Such a soil may be more favourable to the growth of the organism.
3. Hard water may render the bowel more suitable to the growth and activity of the organism.

The probable pathogenesis of the condition has already been described (v pp. 82-83). It would appear that the thyroid enlargement is a defensive process on the part of the body and is brought about thus:-

The gland hypertrophies to meet an increased demand for its secretion, i.e. there is an excess of toxins circulating in the blood and requiring neutralisation.

Another/

Another explanation however may be offered - viz:- For some reason or another in endemic goitre the quality of the thyroid secretion is lowered (v. Iodine content etc. p.80) and the hypertrophy is the effort by the gland to make up for this by an increased output.

When this primary hypertrophy is long continued it is followed by various degenerative changes resulting in the production of various types of goitre.

The disease is probably present in an unrecognised and clinically unrecognisable form in many persons in affected areas, i.e. the cause is present in the system and the thyroid though not enlarged probably shows some increased functional activity with the concomitant histological changes.

Again it is abundantly clear that heredity plays an important part in selecting cases - i.e., that the thyroid apparatus is hereditarily less efficient than normal and therefore less fit to cope with the cause of the disease in members of certain families; and I have also shown that it is possible for such an inefficient gland to become suddenly efficient and, because of hypertrophy, therefore hyper-efficient and productive of severe hyperthyroidism.

Concluding remarks on the Loch Tay Endemic Area.

The Loch Tay Endemic Area is a typical goitre district:- The climate is temperate; it is a mountainous region and most of the cases occur in the most sunless/

sunless parts; there is an abundance of lime and magnesia in the soil and water; it is entirely a rural district, and very largely a region of unprotected water supply; and the people are mainly land workers.

It has been suggested that an estimate of the severity of an endemic may be arrived at from a consideration of the following four factors:-

1. The proportion of cretins present,
2. The value of the factor $\frac{\text{males affected}}{\text{females affected}}$,
3. The tendency of newcomers to the district to develop the disease and
4. The size attained by the individual thyroid enlargements.

As in other goitrous areas in Britain, cretinism and deaf-mutism are practically absent in the Loch Tay Area.

That any one of these factors alone cannot be taken as a true criterion but is only of value when considered with the others is shown by the fact that even in Acharn - where the percentage of cases to total population (being about 15% for the village itself) probably reaches its maximum in the area, the proportion of men affected to women affected is about 1 to 2 (v.p. 39) - one cannot say that the endemicity is high, for most of the cases are confined to a few families with others cropping up singly, or in pairs here and there among the remainder of the population.

As regards the tendency of newcomers to the district to/

to develop the disease there is little that can be said as in a quiet country district such as that under consideration, where there is little coming and going of population, one has little opportunity for studying the question; still I can say that I have never seen a case develop in a newcomer in less than a year, and most of the cases (I have notes of between fifty and sixty) are in old residents, i.e.: persons who have lived the greater part of their lives within the area. I have never heard of cases arising in any of the visitors who come to spend possibly one or two months in the locality in the summer when the goitrogenous agent has been shown to be most active.

Most of the thyroid tumours observed in the area are moderate or small in size and are usually symmetrical parenchymatous enlargements, which afterwards tend to become fibro-cystic. One or two large cystic goitres have been observed, but these are not common.

Judged from these standards therefore the probability is that this agent as it exists in the Loch Tay District is of low virulence and requires continuous administration over a prolonged period of time to produce its characteristic effects.

SECTION X.Recorded Cases.Case I.

Illustrative of Family Predisposition to Endemic Goitre

(see Section IV. A. Page 30).

Case II.

Illustrative of Supervention of Acute Hyperthyroidism
in case of Endemic Goitre. (see Section VI. page 88).

1. Additional notes on this case bearing upon family
predisposition:-

The patient has had the following relations affected
with the condition in its ordinary endemic form:-

Mother, two sisters, two daughters and a son.

Although the family has resided within the goitre
area during the three generations the various
individuals affected have not all resided in the same
part of the area; several have lived in parts highly
affected, others on the fringe of the area where
cases are rare.

2. In connection with this case and in view of the re-
cently expressed opinions regarding the association
between Exophthalmic Goitre and Tubercle -

a. Symptomatically:- "The freely acting skin; the
well nourished hirsute embellishments; hair,
eyebrows, eyelashes; the excellent teeth; the
keen/

keen intelligence; the optimism; the dyspepsias; the tachycardia; and finally the baneful effects which generally ensue from administration of the drug (thyroid extract), combine to produce a picture which is sufficiently convincing" (122); and

- b. Etiologically:- Hollos(123), in a paper entitled "The Tuberculous etiology of Thyreosis" read before the Section of General Pathology and Pathological Anatomy of the XVII International Congress of Medicine this year, maintained that the great majority of cases of exophthalmic goitre were of tuberculous origin, the seat of the infection lying mostly in the apex of the lung or in the bronchial glands in a latent form;

- it is of interest to note that one sister and two of the patient's sons (other than the goitrous son) have suffered from pulmonary tuberculosis, and a grandson from tubercular disease of the bones.

Cases III and IV.

Illustrative of Pulmonary Tuberculosis and Endemic Goitre occurring in the same family:-

Case III : In a family in Acharn, Lochtayside, two sons and two daughters have goitre, one son(non-goitrous) died of pulmonary tuberculosis. The father is goitrous, with symptoms of very slight hyperthyroidism; the mother is/

is non-goitrous, but she has a goitrous sister who has a goitrous daughter.

Case IV : In a family at Lurgloman, Lochtayside (v. Map IV) the mother is goitrous with symptoms of slight hyperthyroidism, a daughter is goitrous (slight), and one of two sons is tubercular (pulmonary).

Case V.

Illustrative of the Treatment of Endemic Goitre by section of the Isthmus (see Section VIII. page 125)

Female : aet. 29; considerable general and probably therefore parenchymatous enlargement of thyroid; symptoms - slight palpitation and dyspnoea; operation advised on account of the increasing size of the gland; isthmus was divided.

The operation was done thirteen years ago and was followed by immediate relief of the symptoms and by a steady decrease in the size of the gland. At the present time the gland is scarcely larger than normal.

Case VI.

Case of two Goitrous Deaf-mute sisters.

(see Section IX. p. 129).

SECTION XI.

Appendix.

A. Endemic Goitre: Further list of Synonyms and Foreign equivalents (after St Lager) (refer to p.3 of Thesis)

French : Gouëtre, goetre, thyreophyme

Latin : Gutteria, botuisgulae

Greek : βρογχοχάλη, γογγρώνη.

Spanish : Papera, papudos, gargantosos, lamparones

Hindustani : Ghega, aubi, Kunthmala

Chinese : Hien, Kien, Jeu, Choei.

in Sennar : Kabinah

in Peru, Chili, Argentine : Papa

in Wallachia : Gusciazu.

B. Result of Analysis of the Durham Goal Water:
(refer to p. 48 of Thesis).

The imperial gallon evaporated to dryness, left of solid matter, dried at 270° F, 94.5 grains:-

{ (Anhydrous) sulphate of lime	31.38	grains
{ Carbonate of lime	15.35	"
{ Sulphate of Magnesia	4.49	"
{ Carbonate of Magnesia	1.48	"
{ Chloride of Magnesia	14.01	"
Chloride of Sodium	6.19	"
Silica	1.28	"
Water retained by salts of Magnesia after drying at 270° F.	16.82	"
Nitric acid, Ammonia, } of each a trace	-	
oxide of iron		
Organic matter and loss	3.50	"

94.50

C, Table of Thymol Solubilities (after Squire)
(refer to p.112 of Thesis).

	1	in	1500	of water
	1	-	190	- glycerin
x	8	-	3	- alcohol (90%)
	8	-	3	- ether
	8	-	5	- chloroform
	1	-	6	- petroleum spirit
	1	-	3	- oil of turpentine
x	1	-	2	- olive oil
	4	-	3	- glacial acetic acid
	1	-	6	- potassium hydroxide.

D. Analysis of Loch Tay Limestone (121)

(refer to p.10 of Thesis).

Soluble in HCl :-	SiO ₂	-	.31	
	Al ₂ O ₃	-	.17	
	Fe ₂ O ₃	-	.97	This corresponds to
	MnO	-	1.94	53.33% of Carbonate
	CaO	-	29.87	of lime and 7.87% of
	Mg ₂ O	-	3.75	Carbonate of Magnesia.

Insoluble in HCl:-

SiO ₂ (TiO absent)	21.53) } Insoluble portion appeared to be largely composed of quartz grains with flecks of mica.		
Al ₂ O ₃	5.06			
Fe ₂ O ₃	1.54			
MnO	.17			
CaO	1.14			
Mg ₂ O	.35			
	CO ₂	-	30.31	
	SO ₃	-	1.51	
Organic matter and moisture			1.34	

99.98

E. Endemic Goitre in School Children in Perthshire:

(refer to p.20. of Thesis).

<u>Highland District</u>	<u>1910-11</u>	<u>1911-12</u>	<u>1912-13</u>
Aberfeldy school	2 cases	-	-
Acharn "	-	1 case	-
Blair Atholl "	-	1 case	-
Butterstone "	-	1 case	1 case
Dull "	1 case	-	1 case
Invervar " (Glenlyon)	1 case	-	-
Pitlochry "	2 cases	-	1 case
Strathloch "	1 case	-	1 case
<u>Western District</u>			
Killin School	1 case	-	-
Thornhill "	-	1 case	-
<u>Eastern District</u>			
Alyth School	1 case	-	-
Blairgowrie School	-	-	1 case
Burrelton "	-	-	1 case
Coupar Angus "	1 case	-	-
Gauldsweil "(near Alyth)	-	-	1 case
Glenshee "	-	1 case	-
<u>Central District.</u>			
Auchterarder School	1 case	-	2 cases
Balgowan School (Methven district)	1 case	-	-
Blairnroar "	-	-	1 case
Crieff "	-	-	1 case
Kinglands "(Logiealmond)	-	-	1 case
Monzie "	-	1 case	-

Perth District (excluding Perth City)

Abernyte School	-	-	1 case
Auchtergaven "	1 case	-	-
Dunbarney "	-	1 case	-
Findo Gask "	-	1 case	-
Glendoich "	1 case	-	-
Kinnaird "	-	-	1 case
Longforgan "	1 case	-	-
Redgorton "	-	-	1 case

F. Origin of Drift Deposits in the Loch Tay District (120)

(refer to p. 10. of Thesis)

"Soil of mica schist in the Tay Valley has been enriched by the carrying of drift deposits from the north west, which has produced a soil derived from disintegration of mica schist and black schist, limestone, Ben Lawers Schist, and epidiorite".

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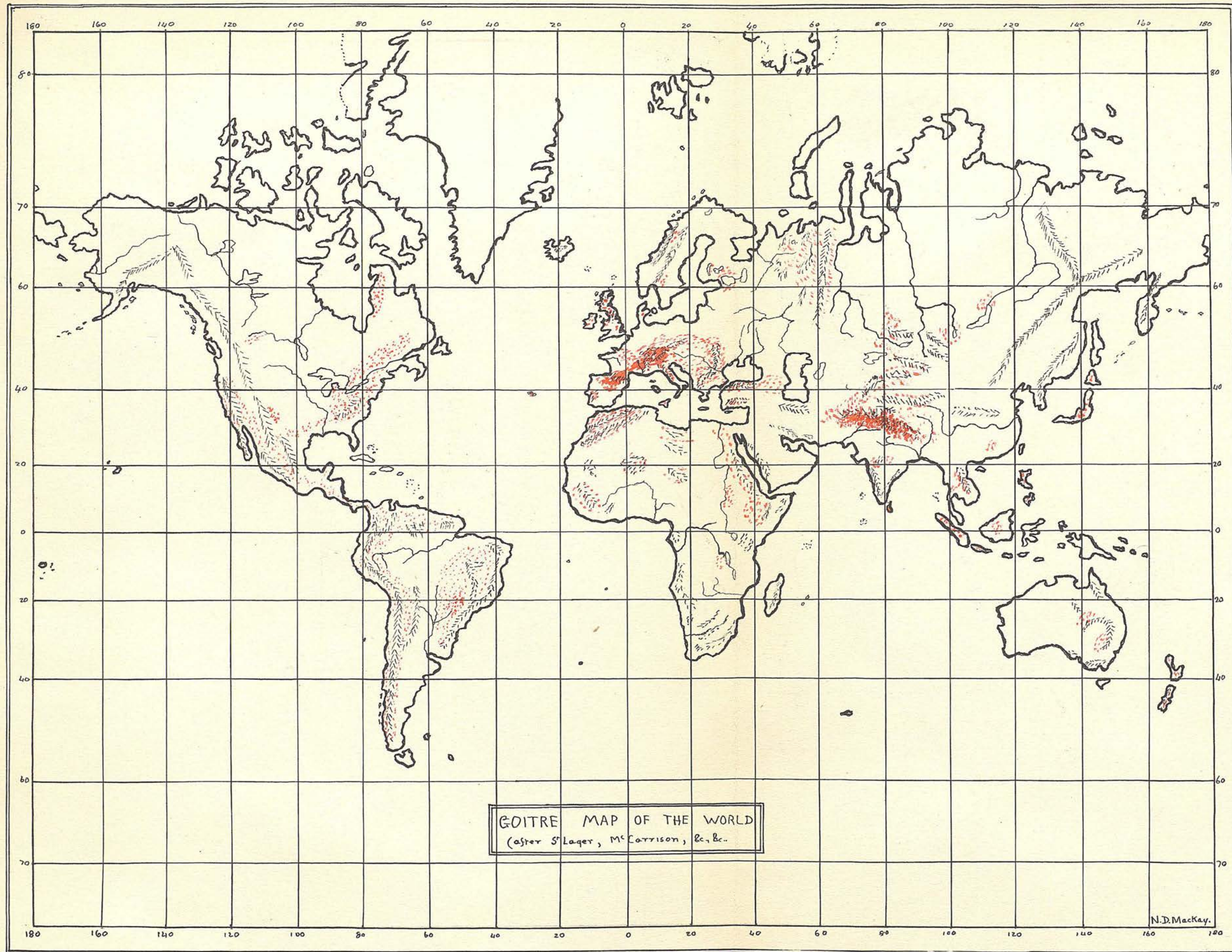
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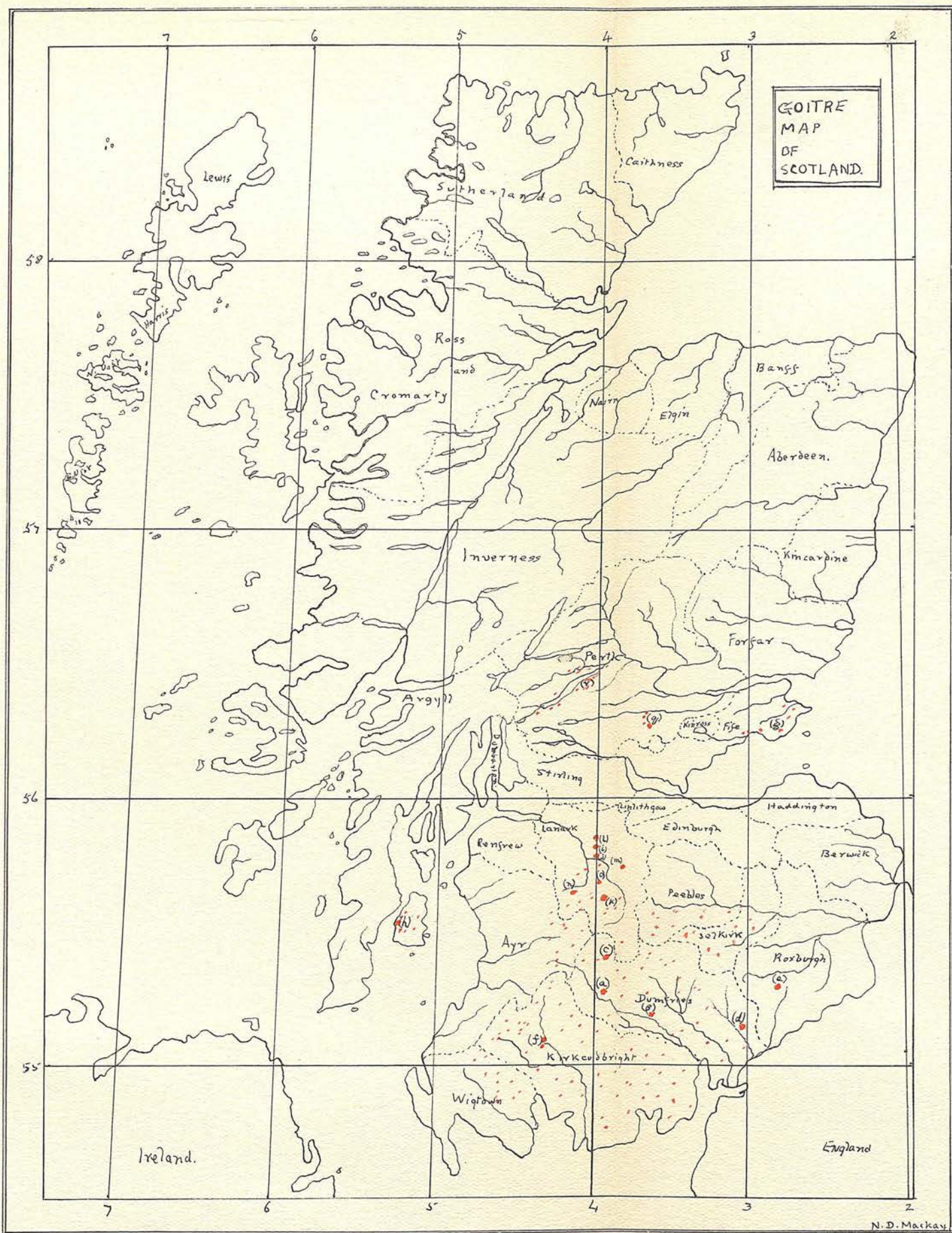
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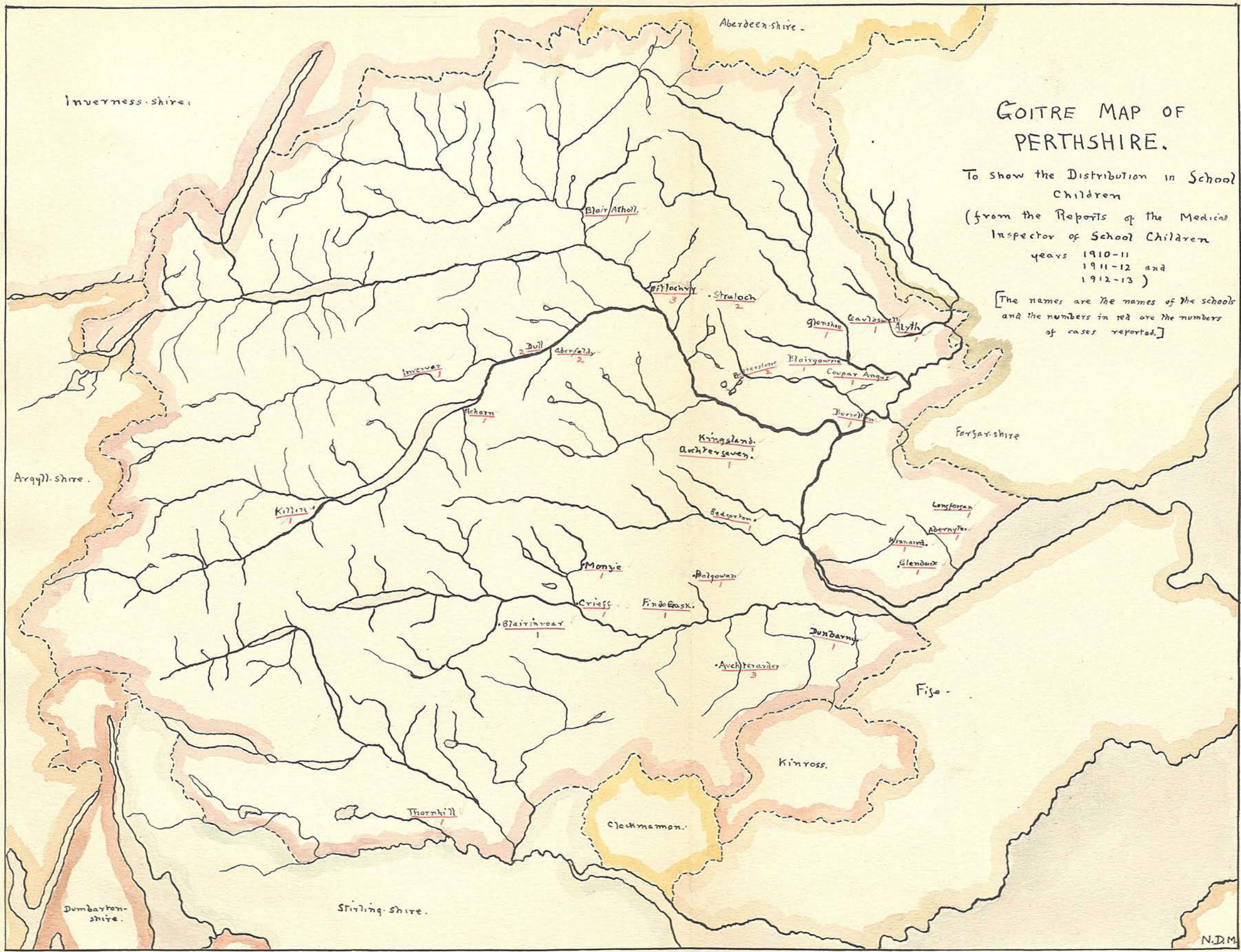
MAP I

(To illustrate Section III of Thesis on Endemic Goitre.)



MAP II.

(To illustrate Thesis on ENDEMIC GOITRE)



MAP III

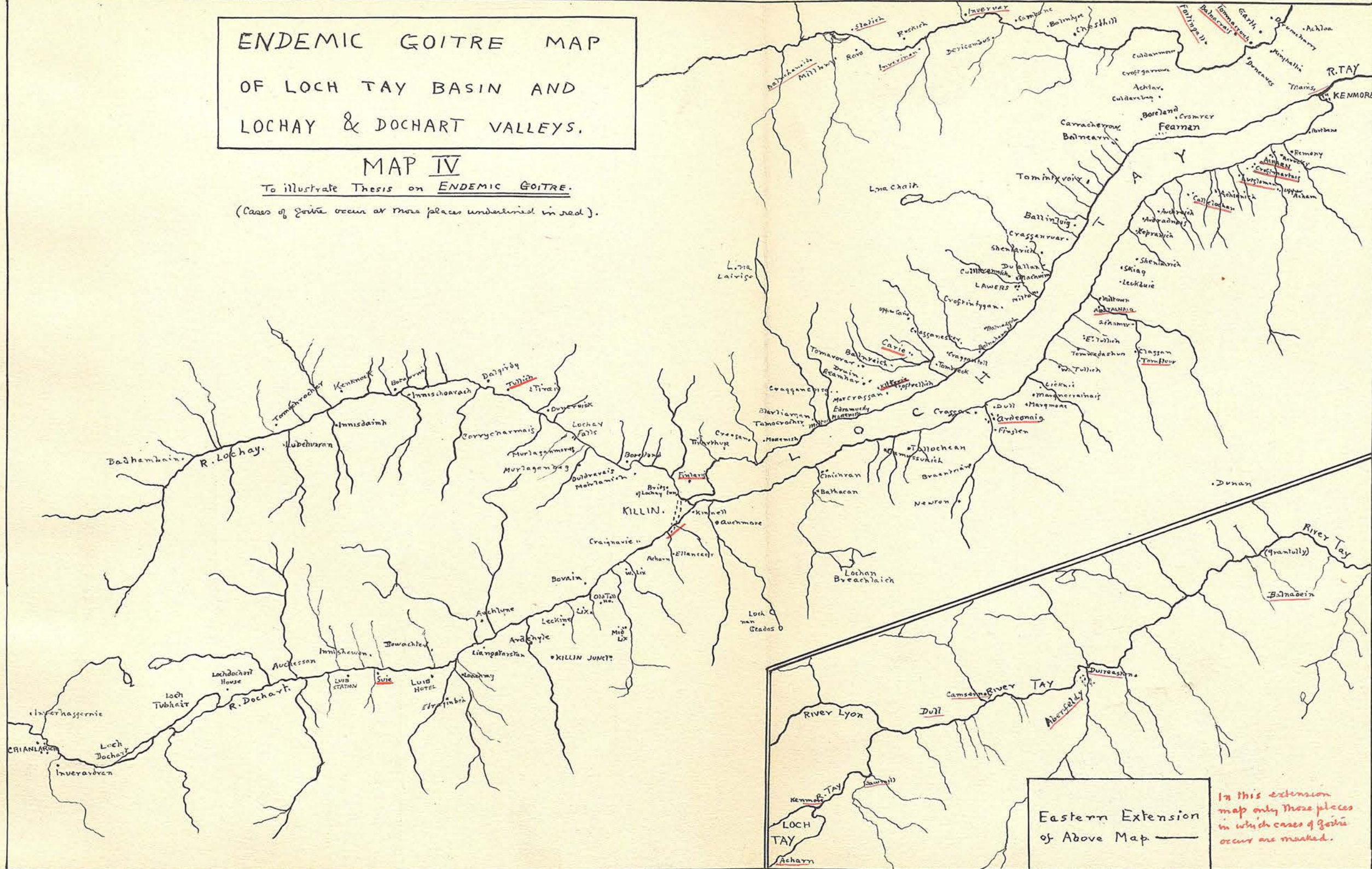
(To illustrate Thesis on Endemic Goitre.)

N.D.M.

ENDEMIC GOITRE MAP
OF LOCH TAY BASIN AND
LOCHAY & DOCHART VALLEYS.

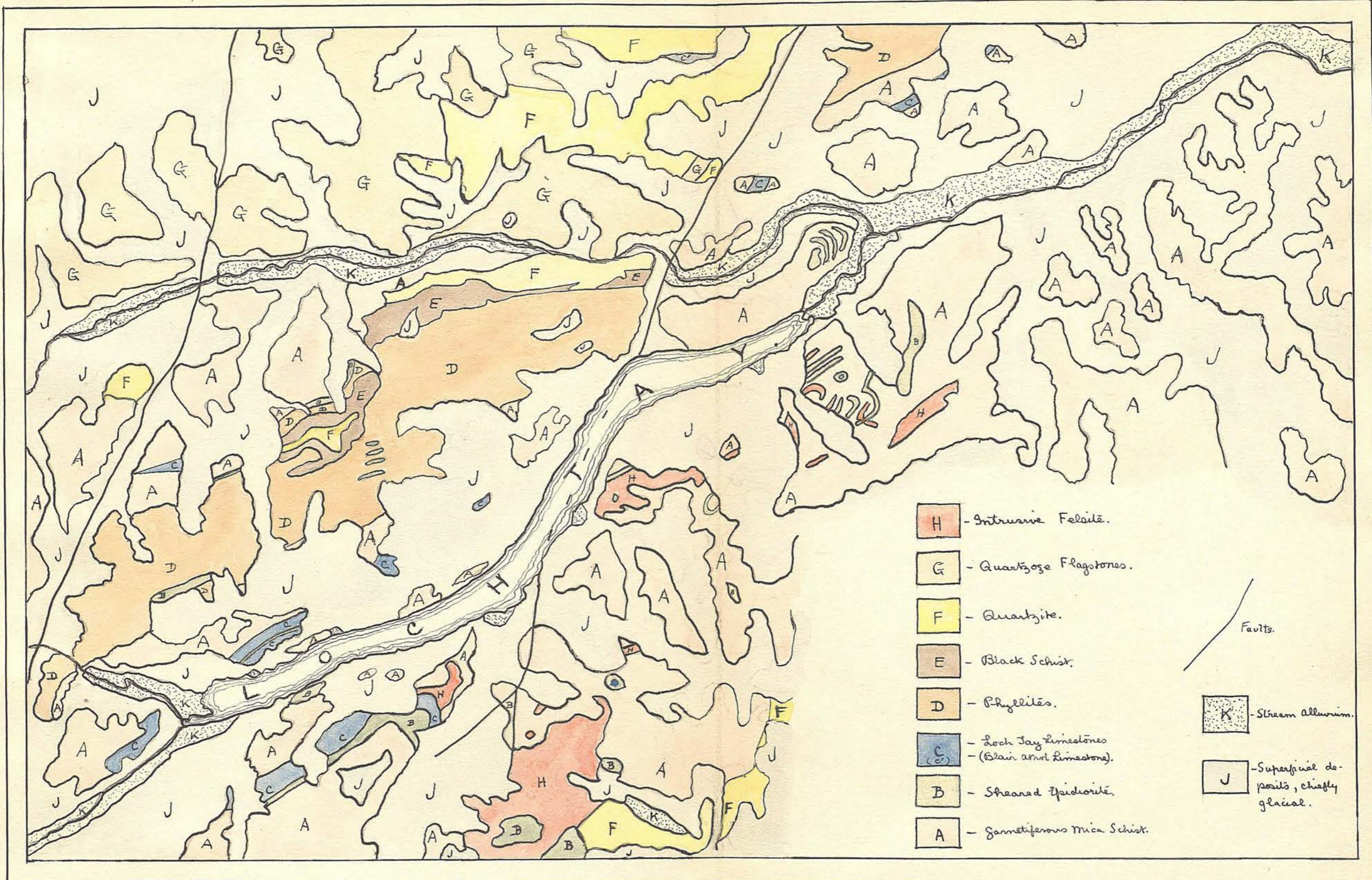
MAP IV

To illustrate Thesis on ENDEMIC GOITRE.
(Cases of Goitre occur at those places underlined in red.)



Eastern Extension
of Above Map —

In this extension
map only those places
in which cases of Goitre
occur are marked.



To Illustrate Thesis on Endemic Goitre.

MAP V

Geology of LOCH TAY AREA.

MAP VI

Diagrammatic Section of above Area.

