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ENDEMIC GOITRE

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CONTRIBUTORS

F. W. CLEMENTS — J. DE MOERLOOSE — M. P. DE SMET
J. C.M. HOLMAN — F. C. KELLY — P. LANGER — S. LISSITZKY
F. W. LOWENSTEIN — W. McCARTNEY — J. MATOVINOVIĆ
S. T. MILCU — J. A. MUÑOZ — C. PEREZ
V. RAMALINGASWAMI — J. ROCHE
N. S. SCRIMSHAW — W. W. SNEDDEN
J. B. STANBURY



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CONTENTS

	Page
Preface	7
History of goitre — <i>P. Langer</i>	9
Prevalence and geographical distribution of endemic goitre — <i>F. C. Kelly & W. W. Snedden</i>	27
Health significance of endemic goitre and related conditions — <i>F. W. Clements</i>	235
Physiology of endemic goitre — <i>J. B. Stanbury</i>	261
The study of experimental goitre — <i>S. T. Milcu</i>	279
Pathological anatomy of endemic goitre — <i>M. P. De Smet</i> .	315
Etiology of endemic goitre — <i>J. Roche & S. Lissitzky</i> . . .	351
Technique of endemic goitre surveys — <i>C. Perez, N. S. Scrimshaw & J. A. Muñoz</i>	369
Therapy and prophylaxis of endemic goitre — <i>J. Matovinović & V. Ramalingaswami</i>	385
Iodization of salt — <i>J. C. M. Holman & W. McCartney</i> . .	411
Principles and problems of endemic goitre control — <i>F. W. Lowenstein</i>	443
Legislation on iodine prophylaxis — <i>J. De Moerloose</i> . . .	453
Index	465

PREFACE

Forty years ago, David Marine, one of the pioneers of mass prophylaxis of endemic goitre, claimed that "Simple goitre is the easiest of all known diseases to prevent . . . It may be excluded from the list of human diseases as soon as society determines to make the effort." Society has still not made that effort, although nothing that has since been learned about endemic goitre has cast doubt on the fundamental validity of Marine's assertion. Public health authorities in many countries have tended to underestimate the importance of endemic goitre as a threat to physical, social and economic well-being; they have lacked conviction regarding the safety and efficacy of prophylactic measures; and they have been deterred by administrative and technical difficulties.

In 1950, the Third World Health Assembly, recognizing the need to stimulate action, recommended that the World Health Organization should undertake a study of endemic goitre and encourage governments to investigate the problem within their territories. A study group on endemic goitre was convened in 1952 and its report was published in a special issue of the WHO Bulletin, which also included a number of original papers dealing with various aspects of goitre control.

The scope of this first WHO publication on endemic goitre was intentionally limited, its object being to make available a number of reports on studies carried out in various parts of the world and not to offer a comprehensive discussion of the problem of endemic goitre control. It was felt, however, that WHO could render a useful service to public health workers, as well as to all those engaged in the study of goitre, by inviting well-known goitre workers to prepare reviews covering all aspects of the subject and collecting these together in a single volume. Plans were drawn up for such a monograph, but by the date set for publication, only six chapters had been received and important gaps remained. As an interim measure, it was decided to publish these six chapters in a second special issue of the Bulletin (1958) and to defer publication of the monograph until additional contributions had been obtained. This has now been done. The present monograph comprises the original six chapters,

revised and brought up to date by their authors, together with six new chapters covering the history, physiology, pathology and etiology of endemic goitre, experimental studies on goitre, practical aspects of endemic goitre control, and legislation on iodine prophylaxis.

Professor W. J. Darby of the Division of Nutrition, Vanderbilt University School of Medicine, Nashville, Tennessee, USA, greatly assisted in drawing up the plans for this monograph. Valuable technical assistance has been provided by Dr F. C. Kelly, Director of the Chilean Iodine Educational Bureau, London, through all stages in the preparation of the material, and helpful suggestions regarding one of the chapters have been received from Professor W. H. Sebrell, Director of the Institute of Nutrition Sciences, Columbia University, New York. To them and to all the contributors who have graciously devoted so much of their time to this undertaking the World Health Organization remains deeply indebted.

It is hoped that this monograph will not only serve as a work of reference for all those interested in the control of endemic goitre but will also encourage the adoption of active measures in those countries where endemic goitre is a considerable public health problem but has not yet received the attention it deserves.

HISTORY OF GOITRE

P. LANGER *

Ancient times

In the light of present knowledge of the etiology of endemic goitre, it would not seem unreasonable to infer that this disorder may have been present from time immemorial among the populations of various parts of the world. Indeed, it seems extremely probable that the etiological agents known to-day (iodine deficiency, nutritional, hygienic, and climatic factors) exercised the same influence in the distant past as they do now.

It is, however, next to impossible to substantiate this presumption with any historical evidence, and consequently we must content ourselves with what references to goitre—often very fragmentary—we can find in the earliest literary sources.

One of the oldest references to goitre is attributed to the legendary Chinese emperor Shen-Nung (2838-2698 B.C.), who, in his book *Pen-Ts'ao Tsing* (*A treatise on herbs and roots*) is said to mention the seaweed *Sargassum* as an efficacious remedy against goitre.^{36, 62} However, there are doubts about the very existence of Shen-Nung as an historical personality. In the book *Huang Ti Nei Ching*, dating from the period 2697-2597 B.C., two types of neck tumour are recognized: those caused by an “accumulation of air” (tumours proper?), and those brought about by an “accumulation of blood” (inflammatory swellings?).¹ Goitre is likewise mentioned in the book *Shan Khai Tsing* (*A treatise on waters and dry lands*), from the period 770-220 B.C., which attributes the disease to the poor quality of the water; and further references are to be found in the literary remains of the Han dynasty (206 B.C. to A.D. 220) and the Wei dynasty (200-264 A.D.), where, along with drinking-water, deep mental emotions and “certain conditions of life in mountainous regions” are arraigned as causes of goitre. The famous Chinese medical writer Ge-Khun, who lived somewhere between A.D. 317 and 419, described a mode of treatment for goitre consisting of *Sargassum* weeds and the weed *Laminaria japonica* Aresch. The

* Endocrinological Institute, Slovak Academy of Sciences, Bratislava, Czechoslovakia

ancient Chinese even used animal thyroid in the treatment of goitre: thus, in the book *Shen Shi-Fan* (420-501 A.D.) mention is made of the use of deer thyroid for this purpose.⁶² Later *Laminaria religiosa* Aresch was used, references to this seaweed dating back to the 12th century. Animal thyroid also continued in use in China, and in the well-known herbal by the eminent Chinese physician Li Shi-Chen (Ming dynasty, 1552-1578) entitled *Pen-Ts'ao Kang-Mu* preparations of pig and deer thyroid are mentioned in the treatment of goitre.⁶² We may well speculate about how much the Chinese really knew of the function of the thyroid and its relationship to goitre.

References to the treatment of goitre with seaweed and even with animal thyroid, both of which have now been established as containing iodine, lend support to the assumption that the disease in question really was goitre, for it may further be assumed that the recommendation of this therapy by ancient authors was based on the purely empirical observation that it was the most efficacious among a whole series of other modes of treatment then in use. It would indeed be difficult to imagine how seaweed and sponges could for thousands of years have entered as ingredients into preparations of remedies against goitre had no favourable results ensued.

Ancient Hindu accounts of medical literature likewise contain references to goitre. Incantations against goitre from the period around 2000 B.C. are found in the Atharva-Veda.⁵ *Galaganda* was the name given by the early Hindu physicians Susruta and Charaka (about 500 B.C.) to tumours of the neck. These tumours are generally considered to have been goitres,^{15, 31, 36} although Greenwald holds a different opinion in spite of the fact that the term *galaganda* is used to this day in India to denote goitre.²⁴

Tumours of the neck were also known in ancient Egypt, where, according to the Ebers papyrus (about 1500 B.C.), they were treated surgically.¹¹ Local applications containing, among other components, salt from Lower Egypt (sea salt?) were used in the treatment of these tumours. It would nevertheless be difficult to decide whether endemic goitre was known at that time. According to Mettler, the operations reported in the Ebers papyrus include thyroidectomy.⁵¹ Wilke, on the other hand, states that no goitres can be identified, either on mummies or on ancient Egyptian paintings.⁷² In this connexion, however, it has to be borne in mind that not even the basic proportions of the body are correctly shown in these paintings. Jantsch³⁶ notes that, according to Pliny,⁶¹ goitre was widespread in Africa, but this is obviously an error due to an inaccurate interpretation of the original text. Greenwald maintains that goitre was unknown in Africa at that period.¹⁹

From ancient times in Western Europe we possess a few accounts by Roman authors that agree about the prevalence of endemic goitre in the Alps. Thus, the poet Juvenal (1st century A.D.) asks: "Quis tumidum guttur miratur in Alpibus?" (Who wonders at a swelling of the neck in the Alps?).³⁸ The architect Vitruvius (1st century B.C.) writes: "Aequiculis

in Italia et in Alpihus nationi Medullorum est genus aquae, quam qui bibunt afficiuntur turgidis gutturibus ” (The Aequi in Italy and the Medulli in the Alps have a kind of water, from drinking which they get a swelling of the neck).⁷¹ With a little imagination Ovid’s words “ Quodque magis mirum, sunt qui non corpora tantum Verum animos etiam valeant mutare liquores ” (And what is more wonderful, there are waters that have the power to change not only the body but also the mind) might be interpreted as reflecting the poet’s impressions on seeing a cretin.⁵⁵ Pliny, too, in the 1st century A.D. touches upon the subject of goitre: “ Guttur homini tantum et suibus intumescit, aquarum quae potantur plerumque vitio ” (Swelling of the throat occurs only in men and in swine, caused mostly by the water they drink),⁵⁸ and in various places in his writings he lists whole series of remedies against goitre.⁵⁹ Ulpianus (2nd century A.D.) writes: “ Tumido gutture praecipue laborant Alpium incolae, propter aquarum qualitatem quibus utuntur ” (The inhabitants of the Alps suffer from a big neck, caused by the quality of the water they drink).³² Caesar is credited with having noted the occurrence of a big neck among the Gauls as one of their peculiarities.^{54, 65}

Works of celebrated physicians of that period often contain descriptions of neck tumours. Nevertheless, the thyroid was not yet regarded as a specific organ and was lumped together with the other neck glands. Goitre was confused with other swellings of the neck (tuberculous glands, lymphadenitis, parotitis, etc.), whence the Greek appellation “ βρογχοκηλη ” (bronchocele) and the very similar expression in Latin “ tumor gutturis ” or “ guttur tumidum ”, which prevailed until the 17th, and to some extent even until the 19th, century.

In Hippocratic writings (4th century B.C.) one finds the expression “ γογγρωνη ” (gongrona), which Ambroise Paré (1150-1590) interpreted to mean goitre (*De gongrona ou bronchocele*), and Littré (1840) also translated as goitre.³⁵ Another Hippocratic expression “ χοιρον ” (choiron) was taken to stand for goitre and was subsequently employed in this sense, for instance by Paulus Aegina (7th century).³¹ “ Botium ” is yet another term sometimes encountered. Thus, Rogerius Salernitanus (12th century) wrote *De cura botii*. The word *struma* was first used by Albrecht von Haller (1708-1777) when he remarked that: “ Strumis longe plerumque thyreoidam glandulam vitiari vulgo notum est ” (It is generally known that goitre is mostly an affection of the thyroid gland).³⁵ These are but a few of the more important expressions to designate goitre encountered in the literature of the past, and many more naturally exist in various languages.

In the well-known Hippocratic treatise on *Air, water and places*, drinking-water is regarded as a cause of goitre (choiron)³¹. Celsus (25 B.C.-A.D. 45) described a tumour (bronchocele) of the neck situated “ between the skin and the larynx that is fleshy only, or may contain a sort of honey-like substance, sometimes even containing small bones and hairs

mixed together", and he recommended incision in its treatment.¹⁵ He was probably the first to attempt to make a distinction between the various forms of tumours of the neck. Galen (A.D. 132-200) also described an operation for goitre, and was even aware of the danger of damaging the recurrent laryngeal nerve. To the glands of the neck (and therefore to the thyroid also), he ascribed the role of secreting a fluid into the larynx and the pharynx.

These views were accepted as late as the 17th and the 18th centuries (even after the discovery of the thyroid as a specific organ), by such physicians, for example, as Bartholin (1616-1680), Malpighi (1628-1694), and Boerhaave (1668-1738).^{9, 36, 66}

We find, however, very little definite information regarding endemic goitre in the medical works referred to above, or in other writings. A plausible explanation for this is advanced by Hirsch, when he remarks that physicians did not formerly gain their experience in localities where goitre may have been widespread, and had in any case little interest in the diseases of populations as a whole.

References to goitre operations are scattered through a great many other works. Thus Leonidas of Alexandria (2nd century A.D.), Aetius de Amida (about A.D. 550)—who was personal physician to the Emperor Justinian I—and after him Paulus de Aegina (A.D. 626-690), all knew about surgical treatment. They differentiated between cystic and solid goitre, the former being suitable for operation, but not the latter because of the copious bleeding. Medical treatment was also used. Galen (A.D. 132-200) and after him Oribasius (A.D. 325-403) both knew of the favourable effects of burnt sea sponge. Aetius de Amida recommended repeated washing of the neck with sea water, or local applications containing sea salt.

The Middle Ages

In the Middle Ages Rogerius Salernitanus (*Chirurgia Rogerii*, 1170), of the Salerno school, Gilbertus Anglicus of the Montpellier school (*Compendium medicinae*, 1240), and Bruno di Longoburgo, a professor at Padua (*Chirurgia magna*, 1252), all described surgical operations for goitre.⁴⁷ Their works show that all of these eminent teachers knew goitre as such and had come into contact with it in the course of their medical practice.

The medical treatment recommended by the ancients for goitre had not been forgotten. Rogerius Salernitanus advised an electuary containing 13 ingredients, among them the ashes of burnt sea sponge.⁴⁷ The use of sea sponge persisted in the literature up to the 19th century. Gabriele Fallopio (1523-1562) obtained successes even with 4-6 spoonfuls of sea water, taken daily over a prolonged period.³⁶ In the Middle Ages goitre was treated in the Alps with preparations concocted from the hypocotyledon of Alpine violets growing in a massive knot.⁷⁰ The resemblance between

certain tumours on plants and goitre was built into a superstitious belief in Northern Bohemia that goitre affected those who ate gall-nuts.⁷ There are a great many of these popular superstitions and customs and it is not possible to deal with them all here. In Bohemia and Germany, for example, it was held that goitre was the result of strenuous work or of frequent fits of coughing, and that it occurred in women after a particularly difficult labour—whence arose the custom of tying a lace round the neck of a woman in labour.³³ A fairly widespread belief in Europe was that goitre is brought on by the effects of the moon. In Ecuador it used to be customary to rub goitres with saliva at the time of the new moon.³¹

During the Middle Ages the most advanced thinkers on medical subjects were the Arabs. One of their greatest surgeons, Albucasis (10th century) differentiated between congenital and acquired goitre. Of these only the latter, in his opinion, was fit for surgery, and then only if it was not too large.^{15, 36, 45}

Endemic goitre was sporadically mentioned. Guy de Chauliac (born A.D. 1300) wrote: “Botium aegritudo regionalis et hereditaria apud multos reputatur” (Goitre [botium] is frequently considered to be a local and hereditary disease), and Lafranchi (died A.D. 1306) considered hard water, especially that found in the Alpine region and in Lombardy, to be the cause of goitre. Arnold de Villanova (1235-1312) left a very interesting piece of advice for those suffering from goitre, viz., that they migrate to another region if less than 25 years of age. He also described goitre in the Lucca province. Later, Valescus de Tharanta mentioned goitre as occurring in the province of Foix.^{32, 36} We may also note that Marco Polo, on his travels across Asia in the 13th century, observed goitre in Yarkand.

Reports of the existence of goitre on the American continent prior to the arrival of Europeans have recently given rise to controversies. Léon⁴⁴ and Lastres⁵⁶ take the expression *coto* or *ccotto*, used by the natives before the time of Columbus, as evidence that goitre did exist in parts of South America at that period. Greenwald, on the other hand, maintains that goitre did not appear in that region before the 17th or 18th centuries.^{18, 24, 27} According to his interpretation the word *coto* originally meant “heap” or “bunch”, and was only later applied to mumps or goitre.

The Renaissance and after

Paracelsus (1493-1541) not only described goitre, but also, in his tract *De generatione stultorum*, attributed the disease to a deficiency of minerals in drinking-water.

A vivid description of endemic goitre and cretinism appears in the treatise *Praxeos medicae*, by Felix Platter (1536-1614) of Basle. “Wherefore,” he wrote, “the disease is frequent in certain regions, in the beginning they write of Egypt, and in Valesia Canton Bremis, as indeed I have seen it myself, and in the Carinthia valley called Bintzgerthal many infants are

wont to be afflicted: who besides their innate simple-mindedness, the head is now and then misformed, the tongue immense and tumid, dumb, a struma often at the throat, they show a deformed appearance: and seated in solemn stateliness, staring, and a stick resting between their hands, their bodies twisted variously, their eyes wide apart, they show immoderate laughter and wonder at unknown things."^a The Zurich chronicler Josias Simmler (1530-1576) described cretins in the canton of Valais, Switzerland, and another Swiss chronicler, Johannes Stumpf (1500-1558) recorded the incidence of goitre in the Grisons at Trimmis, Untervaz, Zizers and Igis. The Dutch physician Pieter van Foreest (died 1597) noted that there were many cretins in the province of Valtellina,^{5, 13} on the Italian side of the Swiss border. In 1601 Johannes Jessenius, a Prague physician, mentioned the occurrence of goitre in various regions (in Bohemia?), and added the strange comment that people considered goitre as a form of adornment.³⁷ In 1736 Gmelin published accounts of goitre occurring in the Lena river basin in Russia.⁵⁴ In Poland, too, descriptions of goitre attributed to the poor quality of drinking-water appeared in 1757.⁴² In the 18th century a remarkable description of endemic cretinism was given by the naturalist H. de Saussure of Geneva, who had observed the condition on his Alpine travels and attributed it to the elevation above sea level and to the quality of the air. Other noteworthy accounts were given by Malacarne (1778) and Ackermann (1790), who visited cretins in their dwellings and ascribed the disorder to advanced stages of rickets. Fodéré (1796) recorded cretinism in Savoy and in the Aosta valley, but rejected rickets as a cause.¹³ Endemic goitre was known in Derbyshire, England, in the first half of the 18th century under the name of "Derbyshire neck".¹⁸

The number of written reports on goitre has multiplied enormously, so that it is not possible to mention them all. It must, however, be assumed that if physicians and even laymen in the past described goitre or any other tumours of the neck, the swellings must certainly have been strikingly conspicuous, arresting the attention at first sight. Goitres of the first or even the second degree, as usually classified to-day,^b probably passed unnoticed, even by physicians, whose interest then lay almost exclusively in curative practice. Perhaps even to-day there are some medical men who do not consider as goitres thyroid enlargements that are hardly perceptible to the eye when the neck is not extended, and refuse to admit that these growths are caused by the same etiological factors as cause large goitres and have the same pathophysiological effects, though perhaps in a somewhat modified degree. Overwhelming testimony from all parts of the world shows, however, that these small goitres are by far the most frequent, and there are regions where massive goitres are relatively rare. But even medium-sized

^a This translation is quoted from Major, R. H. (1939) *Classic descriptions of disease*, 2nd ed., Springfield, Thomas.

^b See the chapters *Pathological anatomy of endemic goitre* on page 315 and *Technique of endemic goitre surveys* on page 369 of this monograph.

goitres, such as occur relatively frequently, may well escape notice in the normal course of everyday life.

In some regions, it is only when the women remove the head scarf that they wear knotted under their chin and undo the collar of their dress that the goitre is exposed and the full extent of the endemic becomes apparent. Even in our own day, such examinations have revealed a striking frequency of goitre in regions hitherto considered free from this disease, and no doubt a similar frequency would have been no less discoverable by these means in the past, especially in temperate and cold climates. Nor can we ignore the efforts, often ingenious, of individuals affected with prominent goitres to hide them from sight, for the deformity attracts notice, brings—and always has brought—mockery upon the unfortunate sufferer, and may at times induce him to shun the company of his fellows. This is especially true of cretins. Cases are known—exceptional, it is true, yet none the less dramatic—of cretins living in stables among farm animals.

These circumstances must be taken into account when interpreting older reports on goitre. Moreover, goitre has never been a killer among diseases, and this too would go to explain why ancient authors devoted less attention to it than to other diseases. It is probable that none of them considered goitre of the first or even the second degree as a disease, especially if it presented no clinical symptoms. Quite the contrary, indeed: such goitres, we believe, were regarded as normal, particularly in women. But there is one most serious obstacle in the way of a correct interpretation of earlier works on goitre, and that is, and no doubt will continue to be, the confusion made between goitre, tuberculous glands, parotitis and other conditions in the neck.

To fill the gaps left by the lack of literary references we might invoke the help of the creative arts, notably painting. It is well known that many eminent painters painted their female models almost exclusively with a swelling of the lower part of the neck that appears to us to be goitre of the first or second degree. A study of goitre in 16th century art was made by Hunziger,³⁴ and De Josselin de Jong¹² referred to the appearance of goitre in pictures by van Eyck, Lucas van Leyden, Rubens and Riemenschneider. Rolleston likewise detected goitre in paintings by Weyden, Dürer, and Rubens.⁶⁶ We are of the opinion, however, that only the first steps have so far been taken to evaluate this rich material. There are cases where a study of ancient works of art may reveal unexpected details, as, for instance, the finding of a picture of a cretin in an old psalter.⁵⁰ On the other hand, it is often difficult to decide whether the swelling depicted is to be attributed to endemic goitre or toxic adenoma, and opinions differ regarding the correct interpretation.

Original, and in themselves very interesting, views, supported by historical studies on the prevalence of goitre in various parts of the world¹⁸⁻²⁸, have recently been expressed by Greenwald, who arrives at the conclusion

that goitre in many countries is only of recent date. His studies show that the history of goitre in some lands resembles the pattern seen in infectious diseases. He postulates an infectious agent for goitre which, he claims, was present approximately 2000 years ago in the Alps, and only in the Alps, whence it slowly made its way into the rest of Western Europe and other parts of the world (America, Africa, New Zealand, the Philippines, Ceylon, etc.), his view being that goitre spread in these regions only after the arrival of Europeans. In many countries its first appearance was marked by severe outbreaks, after which it became less active. The disease resembles leprosy in that it is not, in ordinary circumstances, readily communicable but generally requires prolonged exposure. According to Greenwald, the older reports on swellings of the neck in various countries for the most part describe tuberculous glands or parotitis, and some of the earlier accounts are not reliable enough for an opinion to be hazarded. He admits the occurrence in isolated cases of enlargement of the thyroid, but such instances are not to be confused with endemic goitre. As far as Greenwald's theories are concerned, it is pertinent to observe that not even the best of historical studies will ever provide a solution to these problems, and that the infection theory will have to be corroborated by biological methods.

Anatomy and physiology of the thyroid

In following advances in knowledge of the anatomy and physiology of the thyroid through the Renaissance period, we find a whole series of new concepts springing up. Probably the first person to describe the thyroid was Andreas Vesalius (1514-1564). It consists, he said, of "two glands (glandulas ad laryngis radicem adnatas) one on each side of the root of the larynx, which are large, fungus-like, flesh-coloured, and covered with numerous vessels. The purpose of these glands . . . is to moisten the lumen of the trachea".⁵¹ The first to differentiate the thyroid from the other organs of the neck, however, was Realdus Columbus (1516-1559), who noted that: "Duæ aliae glandulae haerent laryngi asperaeque arteriae, quae feminis sunt quam viris crassiores, hinc laryngis pars prominentior in paucis mulieribus conspicuor est, nam ab earum glandularum crassitie occupatur et sub ea habitat" (Two other glands are attached to the larynx and the rough artery [trachea] and these are larger in women than in men; in few women, therefore, is the protruding part of the larynx more conspicuous since it is rounded out by the thickness of these glands and situated beneath them).⁵⁶ Eustachius (1520-1574) discovered the isthmus of the thyroid. Casserio (1561-1616) considered the thyroid to be one organ made up of two parts without any excretory duct. Great credit for ascertaining the anatomical site, size, and weight of the thyroid is due to Wharton (1614-1673) whose work *Adenographia sive glandularum totius corporis descriptio* (*Adenography or a description of the glands of the entire body*)

(London, 1656), contains this description of the gland: “. . . it contributes much to the rotundity and beauty of the neck, filling up the vacant spaces round the larynx, and making its protuberant parts almost to subside and become smooth, particularly in females, to whom for this reason a larger gland has been assigned, which renders their necks more even and beautiful”.²² This extract gives the impression that the author was used to seeing goitres of the first degree in women, and considered them as normal.

In spite of the fact that anatomically the thyroid was fairly well differentiated, its function was far from being understood. For the most part its rôle, with the other neck glands, was supposed to be to humidify the walls of the larynx, the pharynx and the trachea. At one time it was even considered, by J. Vercelloni, 1711, and Heister, 1717, to be a receptacle for worms.⁶⁶

Schreger (1768-1833) was the first to notice the special blood supply of the thyroid, which he surmised to be a vascular shunt cushioning the brain against a sudden increase in blood flow. Even the anatomist Herbert Luschka (1820-1874) still considered the thyroid to be an elastic cushion protecting the larynx, trachea, blood-vessels and nerves of the neck against direct muscular pressure.³⁶ Merkel (1857), and prior to him Boerhaave and Martin, had taught the view that the thyroid strengthens the larynx and modulates the voice.⁶⁹ Towards the end of the 18th century, however, Albrecht von Haller (1708-1778) had classified the thyroid, the thymus, and the spleen as ductless glands, secreting a special fluid into the bloodstream, and De Bordeu (1776) put forward a theory on internal secretion to the effect that every gland, and similarly every organ in the body, produces specific secretions, which enter the bloodstream and bring about the integration of the entire organism.⁶⁶ But the real function of the thyroid remained hidden until the last decade of the 19th century.

Beside these scientific views flourished a host of non-scientific theses, fallacies, and popular superstitions and customs. In the Middle Ages goitre had been regarded as being a visitation of God, and it is so seen for instance in some legends of the 5th to the 7th centuries.³² Later, the belief spread that goitre could be cured by the touch of the monarch. In France, Clovis I is said to have cured the disease in this manner, and Henry IV, according to his personal physician André Dulaurens (1550-1601),³⁸ caused 1500 goitres to regress by touching the patients and using the formula: “ Le roi te touche et Dieu te guérit.” Many English sovereigns practised a similar custom, and between 1662 and 1682, Charles II is alleged to have “ touched ” 9200 sufferers from the “ King’s Evil ” or scrofula, with which goitre was often confused.² On 20 March 1710, according to newspaper reports of the time, Queen Anne again revived the ancient custom of curing goitre by the imposition of hands.⁵³ This healing power was supposed to be shared by every seventh son of a family,⁷ and it was also thought to reside in the touch of a corpse’s hand, a superstition known even to Pliny.⁶⁰

Towards the end of the 18th and the beginning of the 19th centuries, knowledge about the thyroid made great advances, owing to the efforts of anatomists, physiologists, and clinicians. Studies on endemic cretinism showed that goitre may have been associated with more serious disturbances of this kind, even though the deeper relationships between goitre and cretinism were as yet unknown.

Caleb Hillier Parry (1755-1822) was the earliest to describe exophthalmic goitre, which he first observed in 1786 (the account was published three years after his death in *Unpublished medical writings*).^{47, 66} In 1835 Robert James Graves (1797-1853) published, in the *London Medical and Surgical Journal* a report of newly observed thyroid affections in women, associated with heart palpitations and, in one case, with exophthalmos.

It is claimed that the first man to connect exophthalmos with goitre was the great Persian physician, Sayyid Ismail Al-Jurjani (about the year A.D. 1136).⁶⁶ In 1722 the ophthalmologist Charles Saint-Yves (1667-1736) described 3 cases of exophthalmos accompanied by cardiac pain and slight goitre, but he failed to see any relationship between these symptoms. Some authors think that similar cases had been described earlier by Morgagni (1682-1771), Wiseman (1628-1676), and others. In 1802 Giuseppe Flajani described two cases of goitre with palpitation of the heart. Carl von Basedow (1799-1854) reported a case of exophthalmic goitre in 1840, and drew attention to three main symptoms: goitre, exophthalmos, and tachycardia; and Charcot in 1863 pointed out a fourth one, tremor. In 1886 Moebius set forth the thyrogenous theory of exophthalmic goitre in these words: "Graves' disease is an intoxication of the organism resulting from disturbed thyroid activity". The first metabolic studies in patients with exophthalmic goitre were made by Friedrich Müller in 1893 and two years later Magnus-Levy showed an increased metabolic rate in these patients. This brief historical review of the development of knowledge of thyroid hyperfunction shows that our basic concepts are much less than a hundred years old.

Knowledge of thyroid hypofunction—myxoedema, a term introduced by W. M. Ord in 1878—is of even more recent date, in spite of the claim that Wolfgang Hoefler described it as early as 1657.⁴⁷ The first clear and correct description of myxoedema was given in 1873 by William Withey Gull (1816-1890) as "A cretinoid state supervening in adult life in women".⁶⁶ Not only the physicians, but some surgeons also recognized the existence of hypothyroidism, foremost among them being Theodor Kocher (1814-1917), J. L. Reverdin (1842-1929), and his cousin A. Reverdin (1849-1908).

Some of the experimental work that preceded these concepts deserves mention. A. P. Cooper in 1836 carried out thyroidectomy in puppies, and later observed the dulling of the faculties it caused. Wilhelm Rapp noted certain thyroprival symptoms but ascribed them to operational trauma. Moritz Schiff (1823-1896) was the first systematically to carry out total

thyroidectomy (in 1856-57) on various animals, the majority of which later perished. In 1884 he repeated these experiments, and found that death could be prevented by intra-abdominal transplants of the gland.⁶⁶ These and a host of other experiments showed that the thyroid plays an essential role in the organism. Nevertheless, there were some who categorically denied any function to the thyroid (Munk, 1887; Drobnick, 1888; Arthaud and Magon, 1891), and attributed deficiency phenomena to the injury of adjacent organs, especially the nerves.⁶⁵ However, the decisive factor in the final appraisal of the significance of the thyroid came from the work of surgeons. In 1883, at a congress of German surgeons in Berlin, Kocher reported the changes following total thyroidectomy, the overall picture of which he termed *cachexia strumipriva*. He attributed this condition directly and with absolute certainty to total extirpation of the thyroid, an operation which, from then on, he rejected completely. He stressed the close relationship between cachexia and cretinism, and saw in the loss or impairment of thyroid function a cause common to both. The differences between the conditions, he felt, lie in the fact that cretinism is congenital and hereditary. In September 1882, before the Geneva Medical Society, J. L. Reverdin described his 14 cases of thyroidectomy and, a few months before Kocher, laid stress on the consequences that supervened 2-3 months after the operation. He asked whether some unknown function of the thyroid that had been excised did not enter into play, and from then on decided to discontinue the practice of total extirpation. He recollected that in one case he had removed one lobe only and the ill effects had failed to appear. In April-May 1883, in the *Revue médicale de la Suisse Romande* he noted that the changes he had found to follow thyroidectomy were identical with the myxoedema of English authors, and termed them "myxœdème opératoire". The long drawn out polemic between Kocher and Reverdin as to who had priority in these observations was recently summarized (1951) in detail by Bornhauser.⁵

The 19th and 20th centuries

The 19th century witnessed substantial progress in biological and medical research, supported more and more by objective and precise methods. The number of reports on endemic goitre grew rapidly and great interest was shown in ascertaining the actual prevalence of goitre and cretinism in various regions. The first of these epidemiological studies was, in all probability, dictated by military needs; this was when Napoleon ordered a systematic investigation of goitre because of the large numbers of young men from certain regions who were rejected by recruiting boards as unfit for military duties. He might have been prompted to this step by the vivid impression made on him by the populations stricken by cretinism which he saw at the time of his march into Italy through the Valais.¹³

In 1845, a special commission was appointed by King Carlo Alberto of Sardinia to study the extent of goitre throughout his Kingdom (the provinces of Savoy, Nice, Piedmont, Genoa and the island of Sardinia) and recommend means of combating it.⁶⁸ A similar commission was set up in 1864 by the French Government. Ten years later this commission submitted its report, in which it was recorded that 370 403 persons in France above the age of 20 had goitre, and that in addition there were approximately 120 000 cretins and idiots (the total population of France at that time was around 36 million). At this period, government departments in several countries began to show interest in the prevalence of goitre and cretinism. Statistical reports, based chiefly on conscription records, appeared. In 1881, for example, Sormani published the results of the examination of over 2 million recruits carried out between 1863 and 1876, out of whom 42 863, i.e., 2.09% had been declared unfit because of goitre.⁶⁹ Thus, the widespread character of endemic goitre became evident. Nevertheless, all the writings from this period are characterized by the lack of a uniform criterion for the evaluation of goitre (this still holds true today in spite of the great progress that has been achieved). Differences between the findings of various observers were considerable, and it was practically impossible to make comparative studies without running the risk of reaching paradoxical conclusions. Moreover, most of the studies, being based on military statistics, included only males, who are much less affected by goitre than females.

During the last 50 years, hundreds of epidemiological studies on endemic goitre have been carried out in all parts of the world, and attempts have been made to correlate prevalence with geophysical and geochemical features, as well as with various other environmental factors. These studies are reviewed country by country by Kelly and Snedden in the chapter *Prevalence and geographical distribution of endemic goitre* (pages 27-233), and no attempt will be made to summarize them here.

Realization of the world-wide character of endemic goitre and of its public health importance focused attention on its etiology and on methods of mass prophylaxis. As early as 1867, Saint-Lager⁶⁷ had listed 43 different views on the causes of goitre, expressed by 378 authors. Nineteen of these views attribute the disease to various properties of water, to its origin, or to deficiency or excess of certain minerals; 11 to properties of the atmosphere (humidity, temperature, chemical composition, lack of sunshine or electricity, etc.); 6 to faulty nutrition, poverty and insanitary living conditions; and the remaining 7 to sundry other causes, such as alcoholism and consanguinity in marriage.

The view that goitre is caused by drinking certain kinds of water had been widely held since ancient times, as has already been mentioned. It was generally thought that a high content of certain minerals, particularly calcium salts, was the factor principally involved. A strong advocate of

this theory was Boussingault who, in 1831, drew attention to the significance of a limestone soil in the Cordilleras of New Grenada (now Colombia).⁶ Further studies^{16, 46} suggested that the goitrogenic action of the limestone was due more to the magnesium than to the calcium salts. The part played by minerals in the production of goitre is still unsettled, but experimental work by Hellwig³⁰ and others has shown that, under certain conditions, calcium can exert a goitrogenic action.

A relationship between iodine and goitre seems to have been suspected soon after Courtois isolated this element in 1811 from ashes of the seaweed *Fucus vesiculosus*.¹⁰ By 1816, iodine had already been used in the treatment of goitre by Proust,⁶⁴ and in 1820 Coindet (1774-1848) independently recommended iodine preparations for this purpose. He was prompted to make this suggestion through his discovery that *Fucus vesiculosus* had been used by Richard Russell (1700-1771) in England for the treatment of goitre and that in 1819 iodine had also been found by Andrew Fyfe (1795-1891) in sea sponges, long famed as a goitre remedy. He suspected that iodine was the active substance in both cases. On 25 July 1820, he gave a lecture to the Swiss Society of Natural Sciences in Geneva, in which he described the pathological anatomy of goitre, stressed that the thyroid was an organ *sui generis*, albeit of unknown function, and reported the first results of iodine therapy.⁸ Soon, however, the use of iodine in the treatment of goitre met with marked opposition because of its toxic side-effects (cachexia, cardiac upsets, disturbed menses, subacute and even chronic intoxication). Coindet laid emphasis on correct dosage, for he himself noticed no untoward effects in his 150 patients, whom he kept on low doses. He interrupted medication at the very first sign of intoxication, and later adopted an intermittent form of therapy. Jean-Louis Prévost (1790-1850), however, found that with Coindet's regime certain ill effects still appeared, in spite of every care, and he conceived the idea of a steady reduction in dosage. At the same time, he observed that amounts as low as 0.9-2.0 mg produced a noticeable effect on goitre, from which he deduced that goitre might be caused by a deficiency of iodine or bromine in water and that prophylactic doses of these elements might help prevent its onset. In 1846, together with the Italian, A. C. Maffoni, he put forward for the first time the theory that endemic goitre is due to iodine deficiency.⁶³

The iodization of salt as a method of preventing goitre was first suggested by Boussingault in 1833 (as described by Kelly & Snedden on page 43 in their chapter on the *Prevalence and geographical distribution of endemic goitre*). In 1849, Grange, in a letter addressed to the French Academy of Sciences, recommended the iodization of kitchen salt in the ratio 1: 10 000.¹⁷ During the next two years, the French chemist Chatin published a series of papers describing the results of systematic iodine determinations on air, water, soils, and animal and vegetable foods from various localities in France. On the basis of his findings, he was able to divide these localities into

four zones, in which the incidence of goitre was inversely proportional to the iodine content of the environment. As a protection against goitre, he recommended the supply of foodstuffs from non-goitrous regions, the drinking of wine and pure, running water, the consumption of good food of animal origin, and finally the use of iodized salt. Chatin's work was repeated several times, but with varying results. This is not surprising in view of the extraordinary difficulties involved in the micro-determination of the iodine content of natural substances. Some investigators (e.g., Nadler, 1861) considered Chatin's results to be faulty because they themselves failed to detect iodine in the atmosphere, in water, or in foodstuffs.¹⁴ A tribunal appointed by the French Academy of Sciences reported unfavourably and Chatin's findings fell into oblivion.

Thus far, there had been no real experimental evidence to connect iodine with thyroid metabolism, but, in 1895, Baumann demonstrated that the thyroid contains a surprisingly large amount of iodine and succeeded in isolating from the thyroid a substance which he called "thyroidine", containing 10% of iodine. When used in physiological experiments, this substance brought about the same effect as thyroid itself.³ Oswald pursued the study of the chemical composition of the active substances of the thyroid and isolated thyroglobulin in 1899, and Kendall in 1919 isolated crystalline thyroxine,³⁹ which C. R. Harington later (1926) prepared in synthetic form.²⁹ These studies were decisive in showing iodine to be an essential component of thyroid hormone and paved the way for a renewed interest in iodine therapy and prophylaxis.

The more recent work on the etiology, pathological anatomy and physiology of endemic goitre is discussed elsewhere in this monograph and will not, therefore, be considered here. Attention is particularly directed, however, to the pioneer studies of McCarrison in India on the goitrogenic action of polluted water (see pages 157 and 364) and to those of Astwood, Clements, Greer and others on goitrogens in the diet, especially in vegetables of the *Brassica* genus (see pages 66, 194, 281 and 359). A review of the history of cretinism and a discussion of its relationship to endemic goitre will be found in the chapter by Clements (page 245).

Mass prophylaxis of endemic goitre

Increased knowledge of the geographical distribution of endemic goitre and of its frequency and intensity in various regions, together with a deeper understanding of thyroid function and the causation of some of its disorders, has led to a full realization of the social significance of goitre and of its impact on the health of the community. Although the recommendations made in the last century by Boussingault, Grange, Chatin and others for preventing goitre by the use of iodized salt were largely ignored, the concept of mass prophylaxis by administering minute doses of iodine has steadily gained acceptance during the last forty years.

Present-day practice in the prophylaxis of goitre is based on the teachings of David Marine, who in 1915 declared that "endemic goitre is the easiest known disease to prevent". In the same year, Hunziger proposed that goitre prophylaxis with iodized salt be carried out in Switzerland.

The first large-scale trials with iodine were carried out in 1916-1920 by Marine and Kimball in Akron, Ohio, USA, when they gave to about 5000 schoolgirls, aged between 11 and 18, a daily dose of 0.2 g of sodium iodide in water for 10 days each spring and autumn (4 g of sodium iodide per year).^{41, 48, 49} The results of these trials demonstrated conclusively the prophylactic value of iodine and the absence of side-effects, despite the relatively high doses. Mass prophylaxis with iodized salt was first attempted in Michigan in 1924. In five years, the goitre rate fell from 38.6% to 9%; no toxic effects at all were observed. Nevertheless, the fear of Jod-Base-dow and other side-effects has lingered on and continued to hamper the introduction of iodized salt on a community scale in other areas. Thus, the US Department of Agriculture Bureau of Chemistry insisted on every container of iodized salt being marked with a skull and cross-bones because iodine was considered to be a poison. It was also feared by some surgeons that the use of iodized salt would bring an epidemic of exophthalmic goitre in its train. Many families refused, on various grounds, to use iodized salt, and an attempt to enforce its use by federal legislation failed.

In spite of these difficulties, the consumption of iodized salt gradually increased in the USA, and during the 1920's the iodization of salt began to be practised also in Switzerland and in the Valtellina province of Italy; Canada, the Netherlands, New Zealand, Poland and certain parts of Germany followed a little later, and, more recently, iodized salt has also come into use in some states of Central and South America.

Further details of the early trials with iodized salt and of the administrative and legal problems encountered will be found in Kimball⁴¹ and in the chapters specifically devoted to these questions in this monograph (see pages 386, 404, 411 and 443).

In concluding this historical survey—which makes no claim to being a comprehensive study of the subject—it should be pointed out that to date no serious objection has been raised against iodine prophylaxis although the universal and absolute validity of the iodine-deficiency theory has often been questioned. Today, we possess an abundance of reports from all parts of the world on the favourable effects of iodine prophylaxis, and if this method were universally adopted, it would appear possible at least to achieve a great reduction in endemic goitre in the world, if not to eradicate it completely. This requires, however, concentration of effort and a long-term, co-ordinated follow-up of the effects of prophylactic treatment.

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