THE FIRE OF LIFE (THE THYROID GLAND)

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Anatomy of the thyroid gland

ANDREAS VESALIUS (1514–1564)[1] was probably the first person to describe the anatomy of the thyroid gland, saying "it consisted of two glands, one on each side of the root of the larynx, which are large, fungus-like, flesh coloured and covered by numerous vessels". However, great credit is due to Wharton (1614–1673)[2] for describing the site, size and the weight of the thyroid gland. The thyroid gland is situated in front of the neck deep to the infrahyoid muscles. It consists of two lateral lobes, one on each side of the thyroid-trachea complex, and joined together by the isthmus. Frequently, especially in goitrous states, a pyramidal lobe is present, arising from the upper border of the isthmus and extending to variable length upwards to the hyoid bone, Figure 1. It is a very vascular organ. It has no duct but discharges its secretion directly into the blood stream, hence it is called an endocrine gland. Taylor[3] found that the normal weight of the thyroid gland in Western Nigerians varied from 7 to 21 gm. with a mean of 13 gm. Generally, it weighs between 20 and 25 gm, in the Caucasians.

The function of the thyroid gland

The mode of function of the thyroid gland was not known for many centuries. Cooper[4] in 1836 experimentally removed the thyroid glands of puppies and later observed the dulling of the faculties that occurred in the animals. Moritz Schiff[5] performed total thyroidectomy (complete removal of the thyroid gland) on various animals between 1856 and 1857 and noted that majority of the animals later died, but he discovered that intra-abdominal transplantation of the gland prevented death of the thyroidecto-mised animals. However, the final decisive appraisal of the significance of the thyroid gland was made by the surgeons. Kocher[6] and Reverdin[7] separately reported that removal of the thyroid gland, *in toto*, (total thyroidectomy) in a human subject resulted in a state whereby the person gradually became dull, apathetic, sluggish
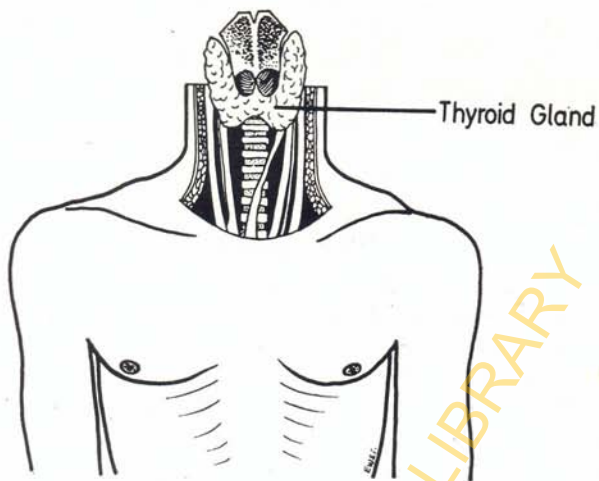
Fig. 1. The Thyroid Gland in situ.

both in thinking and speaking, constipated, overweight and infertile. The body temperature fell and the person was intolerant of cold. The heart slowed down. Indeed the FIRE of LIFE of such a person has been extinguished by complete removal of the thyroid gland. This state of low thyroid gland function is called hypothyroidism or myxoedema.

The normal thyroid gland produces hormones which are essential to maintain normal life ! Iodine is the main ingredient, or if you like, the firewood or petrol of the thyroid hormones. The organic iodine of the diet is generally reduced to inorganic iodide before absorption into the blood stream. The absorbed inorganic iodide is either excreted mainly by the kidneys or taken up or trapped by the thyroid gland. Thiocyanate and perchlorate ions prevent iodide trapping and also cause the discharge of the iodide which is not chemically bound by the thyroid gland. The trapped iodide in the gland is oxidised and it immediately attaches itself to a tyrosyl residue to form monoiodotyrosine (MIT). Condensation of two MIT residues forms di-iodotyrosine (DIT). The monoiodotyrosines and di-iodotyrosines are incorporated into the thyroglobulin within which further condensations and regrouping result in the formation of tri-iodothyronine (T3) and thyroxine (T4), Figure 2. The T3 and T4 are carried in the thyroglobulin and released into

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the blood stream as needed, Figure 3. Thyroxine constitutes about 60 to 90% of the circulating iodine though tri-iodothyronine is more potent than thyroxine unit for unit. The iodotyrosines (MIT and DIT) are deiodinated and their iodine recycled through the iodine pool within the gland.
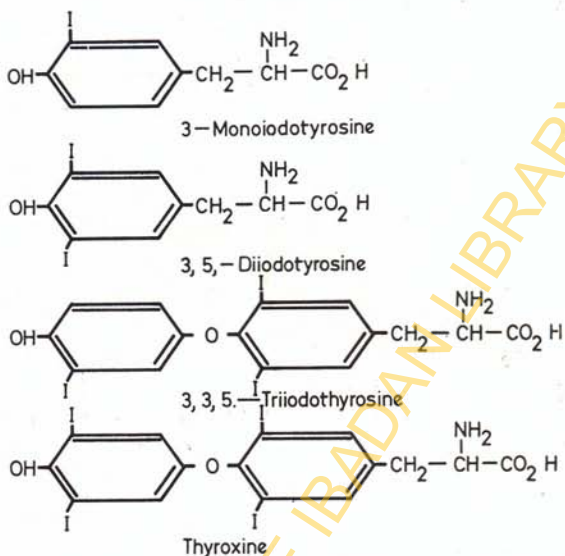

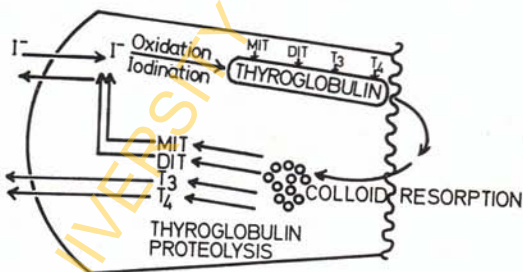Fig. 2. Formulae of the stages of thyroid hormones synthesis.

Fig. 3. Diagramatic intracellular thyroid hormones synthesis.

Normally, the thyroid gland secretes between 100 and 200 ugm of hormonal iodine per day and this is turned over in the periphery at the rate of approximately 10% per day. Although the precise

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mechanism or mechanisms of hormonal action is still not clearly defined yet it is known that the two hormones act by stimulating oxygen consumption in the cells of certain tissues such as the liver, heart, kidney, epidermis, diaphragm, gastric mucosa, pancreas, salivary glands and skeletal muscles. This effect is probably secondary to increase in protein synthesis. More recent evidence[8],[9],[10] suggests that the presence of the mitochondria is essential for the occurrence of the stimulating effect on protein synthesis. It has been shown that thyroid hormones profoundly affect the function and structure of mitochondria both *in vivo* and *in vitro.* The hormones alter the activities of mitochondrial enzymes, affect mitochondrial capacity for oxidative phosphorylation, produce mitochondrial swelling and increase both the number of mitochondria per cell and the number of critae per mitochondrium. The hormones stimulate mitochondrial incorporation of aminoacids into proteins and increase oxygen consumption by mitochondria of sensitive organs. It is most probable that the thyroid hormones produce their effects upon the mitochondria as a result of a primary interaction with the mitochondrial membranes through the agency of an unidentified product of their reaction to stimulate ribosomal protein formation.

Control of thyroid secretions

The thyroid gland is under the control of the anterior lobe of the pituitary gland which secretes the Thyroid Stimulating Hormone (T.S.H.). Thyroid Stimulating Hormone is an essential stimulator of all the stages of hormonogenesis, the release of the hormones and most probably the cellular phase of iodine metabolism. The rate of secretion of the T.S.H. varies inversely with the concentration of thyroxine (T4) circulating in the blood stream. Thus there is a hormonal negative feed-back mechanism between the pituitary and thyroid glands, the Pituitary-Thyroid Axis of Salter. The secretion of T.S.H. is also controlled by the brain through the hypothalamic chemoreceptors which produce a Thyrotropin-Release-Factor (T.R.F.) to stimulate the pituitary gland to release T.S.H. Thus the secretion of T.S.H. is governed by two interacting forces, viz. Hypothalamic drive on the thyrotrope cells mediated by the T.R.F. and the feed-back inhibition exerted by T4 directly

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on the pituitary gland. The originally defined pituitary-thyroid axis can now be modified to the more complex system: the hypothalamic-pituitary-thyroid triangle.

Disease of the thyroid gland

It is obvious from the foregoing accounts that the thyroid gland function may be hormonally deranged in two important ways:
1. the gland may fail to produce enough hormones, and
2. it may produce too much of them.

More commonly, however, the thyroid gland may become enlarged without demonstrable hormonal dysfunction. Also, the gland may be affected by diseased conditions that affect any other body tissues with variable hormonal effects. In nearly all cases, any disease that affects the thyroid gland causes its enlargement. An enlarged thyroid gland, due to any cause, is known as a GOITRE.

Hypothyroidism

Just as fire is essential for a fuller and richer life, so is the thyroid gland essential for the maintenance of normal body functions. Indeed, the thyroid gland is the Fire of Life!

When the thyroid gland is absent or produces little or no active hormones, the fire of life is not lit at all or it burns very lowly. A child born in such a state fails to develop physically and mentally, the features are coarse, the lips are thickened, the tongue is too big for comfortable accommodation within the mouth, the child cannot speak early and clearly or not at all, it is cold and uninteresting. Many such a child perishes early in life. If it survives, it remains a child all his life and becomes the village idiot or imbecile. This child is a cretin, a pariah of what is supposed to be created in the image of God.

However, a child may suffer from milder degrees of hypothroidism. The child is usually stunted in growth physically and has a low I.Q., Figure 4. The bones remain immature, the heart beats slowly, the bridge of the nose may be depressed, he is deaf or deaf and dumb, he may have opaque lenses with resultant poor vision. He is usually anaemic and succumbs easily to minor childhood illness. In this child the fire of life is burning weakly. Traditionally, the thyroid gland has not been considered essential to life,

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but the sight of a cretinous child or an adult in the depths of myxoedematous coma, or even the examination of an unmetamorphosed thyroidectomised tadpole emphasizes how grossly abnormal life without a thyroid, indeed life without a fire, can become.
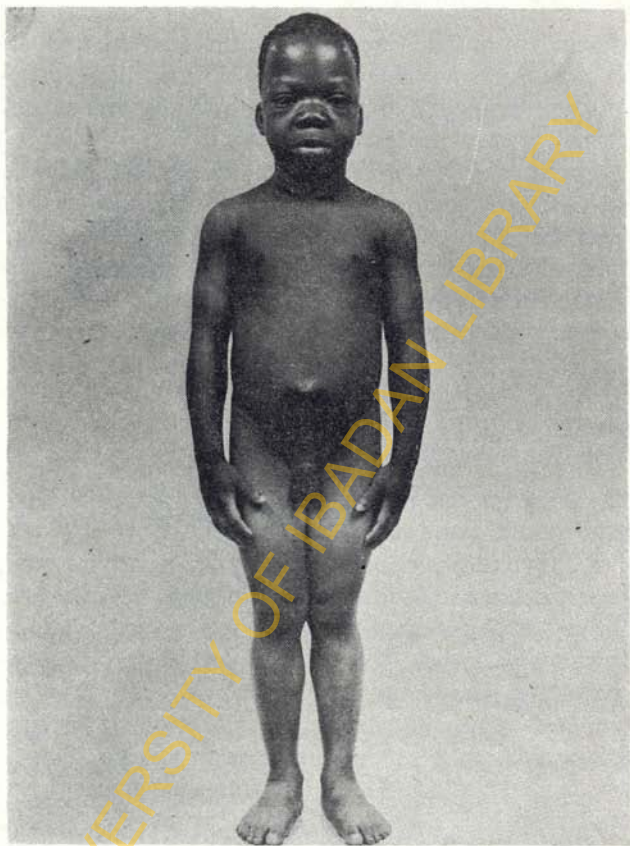

Fig. 4. An underdeveloped twelve-year old boy suffering from thyroid hormone deficiency: hypothyroid state.

Hyperthyroidism

If, on the other hand, the thyroid gland produces more hormones than required for healthy living, the fire of life burns furiously and consumes everything in its path. In such a state, there is overactivity of almost every organ in the body. The afflicted person, often a

woman, becomes excitable, irritable and restless; she sweats profusely, sleeps poorly and though appetite is greatly increased and she consumes enormous amount of food yet she loses weight. Her heart beats rapidly and loudly, she is hot and is intolerant of heat, the hands are tremulous like leaves in a gentle wind, menstruation may at first be profuse but eventually ceases, her eyes become bigger and almost popping out of the head, the reflexes are quicker and in about 95% of cases the thyroid gland is enlarged. This state is known as hyperthyroidism. It may occasionally affect children, Figure 5, though it is commoner in adults, women more often than men, between 20 and 30 years, Figure 6. It may also occur in older people.
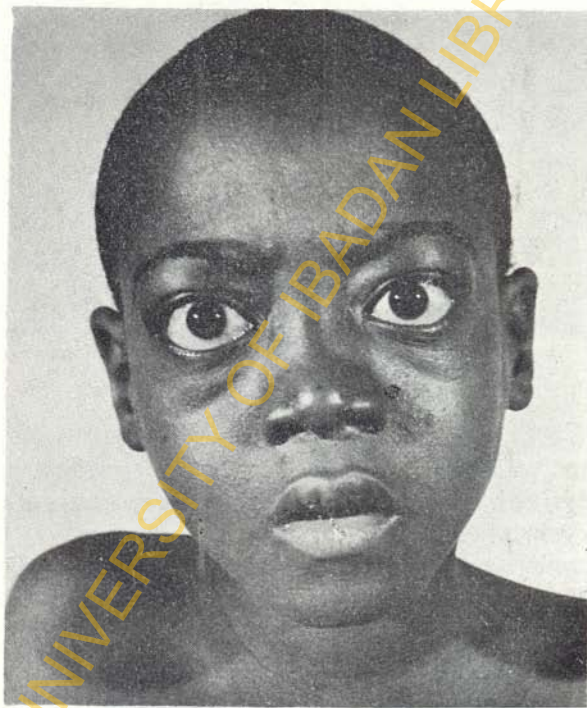

Fig. 5. A nine-year old boy suffering from hyperthyroidism. Primary thyrotoxicosis. Note the bulging eyes.

Primary cancer of the thyroid gland is quite common, the incidence being about 12% in the U.C.H. In a great majority of cancerous cases, the thyroid function is hormonally normal. In a few
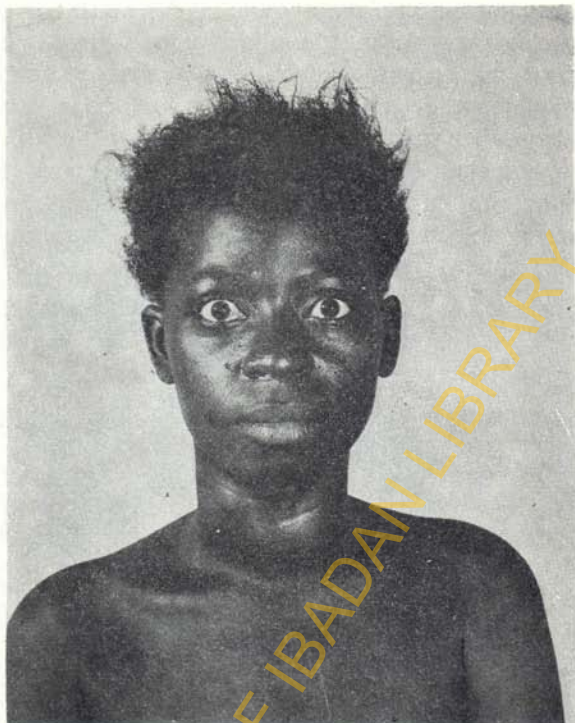
Fig. 6. *A young woman suffering from hyperthyroidism.*
Note the protruding eyes.

cases (3–5%), however, primary cancer of the thyroid may be associated with hyperthyroidism. In fewer cases, still, a primary cancer may be hormonally neutral and yet the secondary deposits of the cancer in other parts of the body may be active and produce so much hormones as to cause hyperthyroidism, Figures 7a, b & c. Theoretically a cancer of the thyroid can destroy the whole gland and thus lead to hypothyroidism but this must be exceedingly rare. I have not seen one such case.

The Simple Goitre

By far the most common malady of the thyroid gland is the simple enlargement of the gland. The simple goitre, by definition, is not associated with hyper-activity or hypo-activity of the gland and it is not cancerous. Olurin *et al.*,[11] found that simple goitre

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constituted about 85% of all cases of thyroid gland diseases in the University College Hospital, Ibadan. The degree of simple enlargement of the thyroid varies considerably. It may be small, Figure 8; it may be averagely enlarged, Figure 9; it may be big, Figure 10 and it may be a giant simple goitre, Figure 11.

The causes of simple goitre are many. However, the commonest cause of simple goitre is chronic or prolonged iodine insufficiency. When the normal thyroid gland fails to obtain sufficient amount of iodine to form T3 and T4, the blood levels of these hormones fall. Through the agency of the hypothalamic-pituitary-thyroid feedback mechanism described earlier, the fall in blood T4 stimulates the pituitary both directly and indirectly to increase the production of T.S.H. The T.S.H. normally stimulates the thyroid gland to produce T4 as required but in the absence of adequate iodine, the
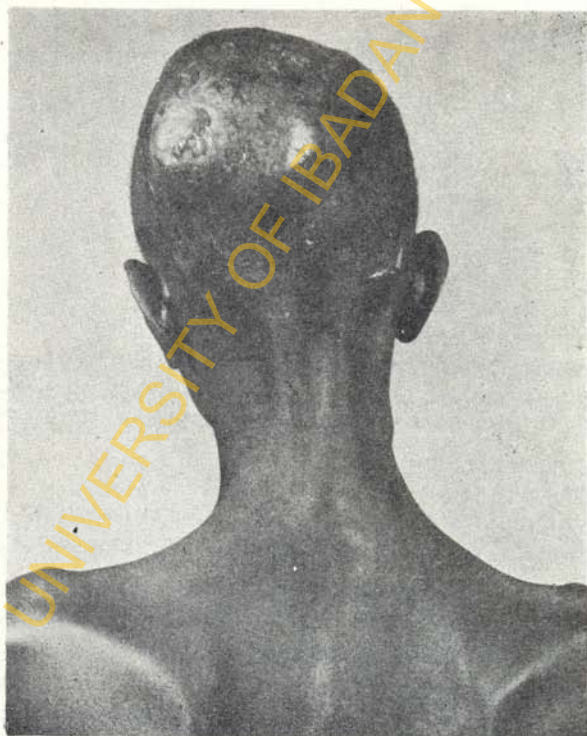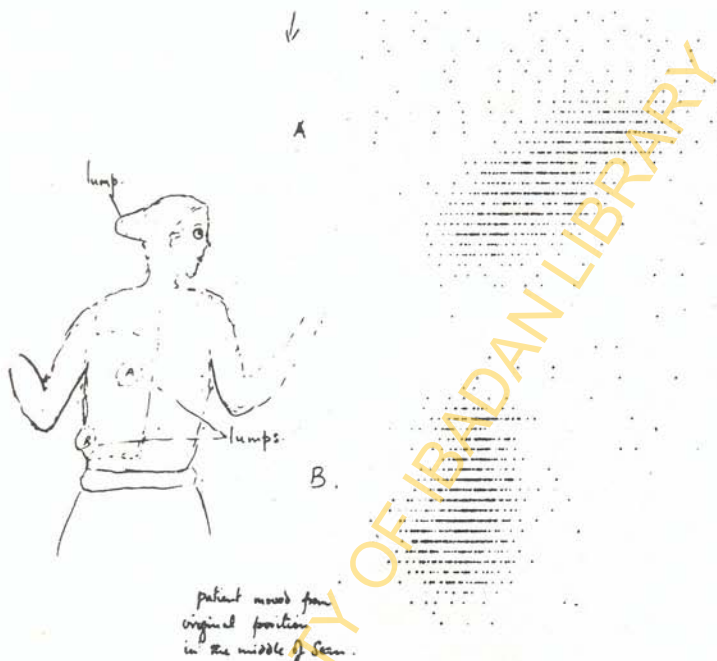

Fig. 7. (a) Active secondary cancer deposit on the skull.

Fig. 7. (b) *Scintigrams from same patient showing that the secondary deposits in the ribs and skull have taken up radioiodine: evidence of hormonal activity of secondary deposits.*

thyroid gland responds to this stimulus by increasing the number and size of its cells. The ultimate effect of prolonged stimulation is an increase in the weight and size of the thyroid gland in an attempt to produce more hormones. Thus the iodine deficiency goitre is an adaptation of the gland to chronic or prolonged iodine deficiency.[12] The natural source of iodine is the soil, water and air and the average daily iodine intake is about 100 ug. It follows that goitre will be common in any population which lives in an area

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Fig. 7. (c) Drawing to dramatize the features of 7 (a & b).

where the soil and water are deficient in iodine. When goitre occurs in at least 10% of a population it is called "endemic goitre"[13] and the area is declared a goitre endemic area.

Endemic goitre has a world-wide distribution. It occurs predominantly in mountainous districts. The geochemical explanation of this association of endemic goitre with granite mountains is that during the last Ice-Age, the glaciers washed away the earlier soil, and subsequent new soil making material were generated by grinding up undifferentiated pre-Cambrian granites containing little or no iodine. The soil and the water in such mountainous areas contain very little or no iodine. The most notorious goitre areas of the world are found in high mountain regions: Alpine valleys, Pyrenees, on the slopes of Himalayas and along the Cordillera of the Andes.
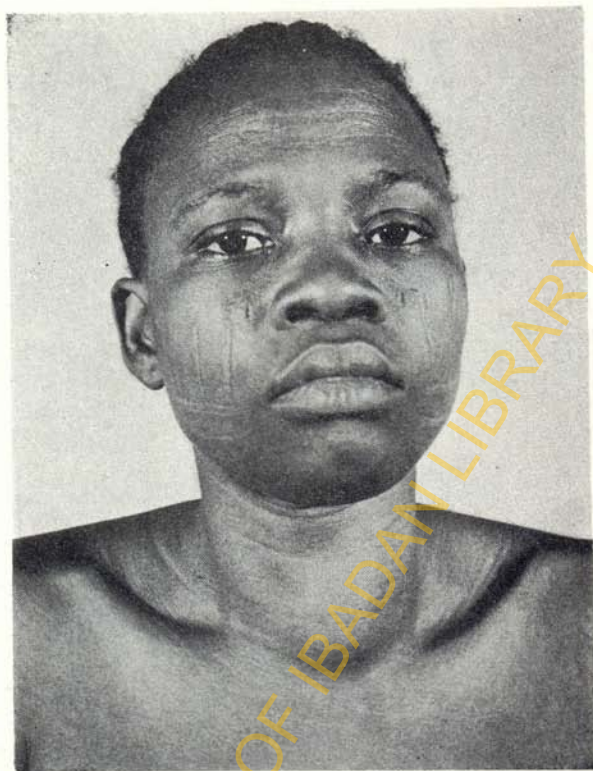
Fig. 8. Small Goitre

Very little is known about the incidence of goitres in Nigeria. Tomkin[14], in his travels through Nigeria in 1905, found that 20% of the population of a village called Gitata north of Keffi in Benue-Plateau State had goitre. The first really scientific goitre field survey in Nigeria was reported by Wilson in 1954.[15] She found that 46% of the people living in Zagun near Jos had goitre and she correlated this high goitre incidence with low iodine content of their water supply. Wilson also mentioned a number of places in Nigeria which she said had endemic goitre, Figure 12. She, however, stated that she did not carry out field surveys in the latter areas and therefore she did not know the real incidence of goitre in those places.

Nwokolo, Ekpechi and Nwokolo (1966)[16] conducted detailed goitre field surveys in some parts of Eastern Nigeria. They found

endemic goitre in many towns and villages in the northern part of Nsukka district, the incidence varying from 27% to 59% in adult women and to lesser degrees in men. They also reported endemic goitre in adults and school children in Ogoja and Obudu districts. Ekpechi[17] found that the water supplies of these areas of endemic goitre were deficient in iodine.
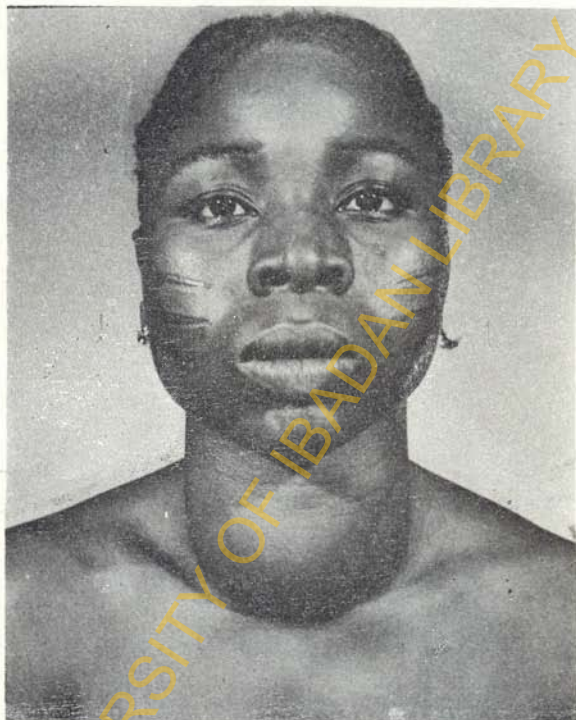

Fig. 9. Moderate Goitre

In a Nutrition Survey of Nigeria by the Department of Health Education and Welfare of the United States of America,[18] the investigators found 17.9% small goitres prevalence in Lagos, 14.7% prevalence in Nsukka children and 9.1% in Asaba children. They also found 13.6% goitre prevalence in the Savanna North, 10.4% in some areas of the Benue-Plateau State, 11.9% in the Urban Federal District and 9.9% in the rain forest areas. They did not however, give details of the specific areas referred to in these broad regional classifications.
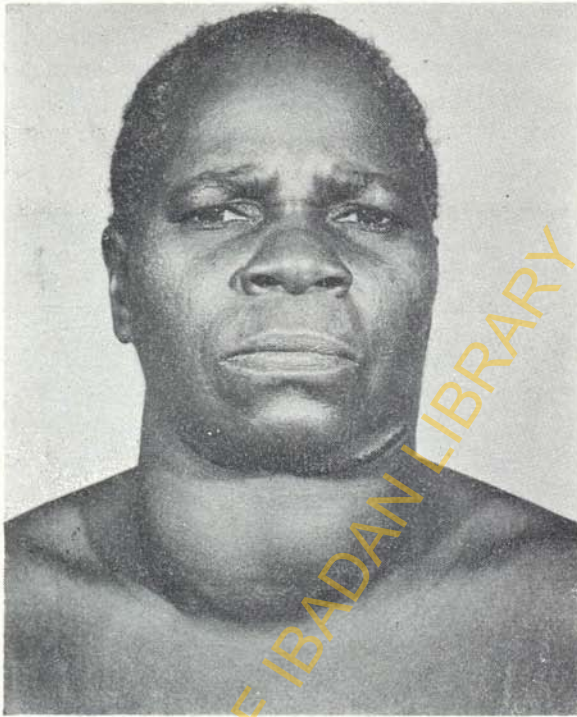
Fig. 10. Big Goitre

During a four year-period, 1970 to 1973, I personally carried out a number of goitre field surveys in many parts of the Western and Midwest States of Nigeria. Many towns and villages were randomly selected for the surveys. In the selected places, as many people, adults and children, as were available were either examined in their homes or gathered in town halls, village squares and market places, Figure 13, and examined. Schools were visited wherever possible and the children in attendance were examined. The method of examination consisted of inspection and palpation of the neck of each subject. The total body weight, height and circumference of the neck of a large number of people were measured. People were questioned about their diet. The sources of the local water supplies were visited and many samples of the water were

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brought back to Ibadan and analysed for their iodine contents. Local market places were visited to study the common food items exhibited.

The surveys entailed extensive travelling. I am greatly indebted to Professors Adadevoh and Osunkoya for lending me their departmental Land Rover estate car shown in Figure 14 during a lunch break! I must take this opportunity to express my gratitude and
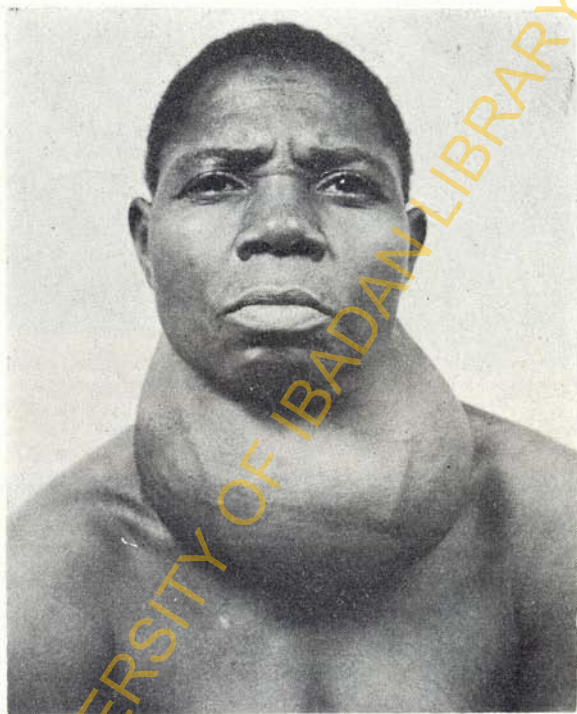

Fig. 11. Giant Goitre

appreciation to the many kindly and progressive Obas, Chiefs, Teachers, Council Officials and many ordinary people who were kind and helpful to me and my team in every place we visited. They made our job easier and enjoyable.
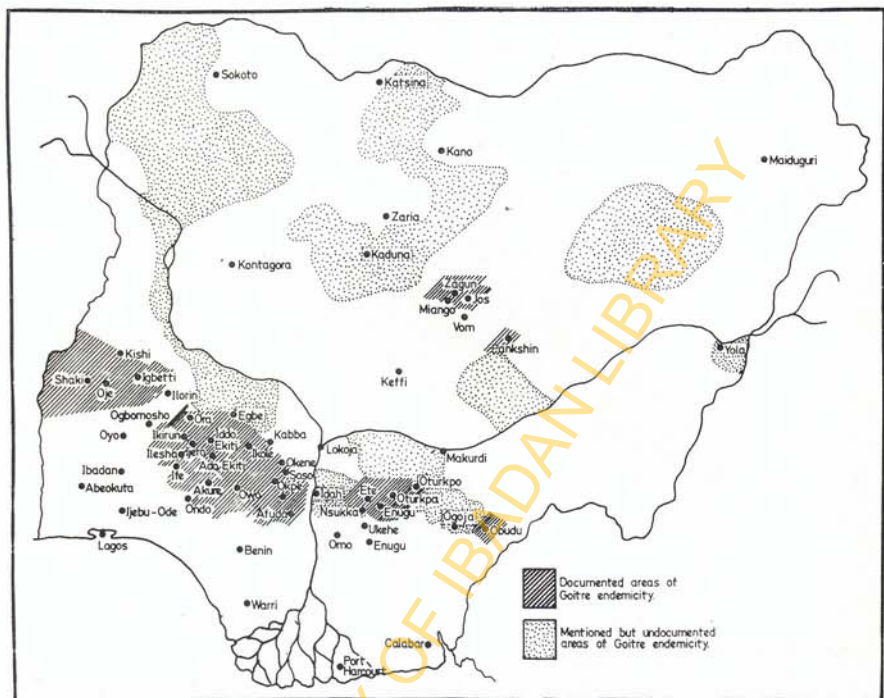
Fig. 12. Map of Nigeria showing surveyed (dark shades) Goitre endemic areas and unsurveyed (light shades) supposed goitre endemic areas.
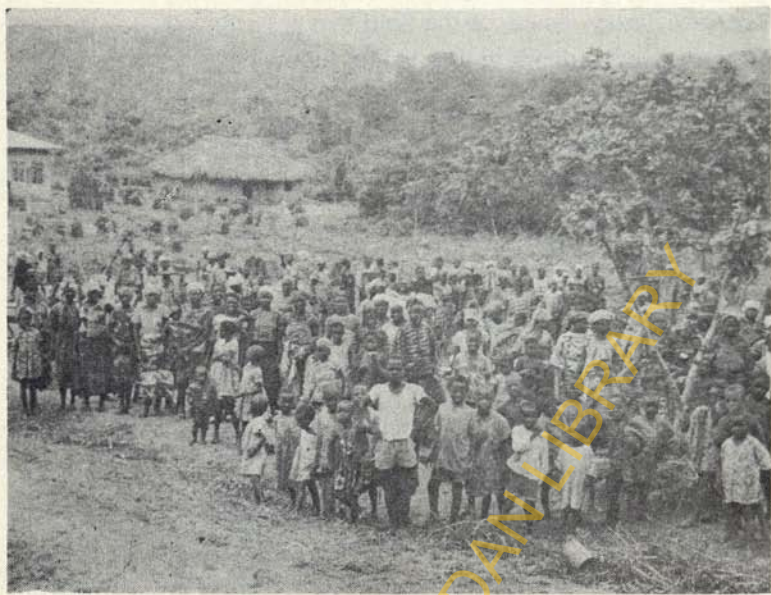
Fig. 13. Villagers gathered in market place for examination during field survey. Place: a small village in a valley surrounded by granite rocks between Igara and Ososo.

Fig. 14. A "lunch break" near Ikole Ekiti.

The preliminary results of the field surveys showed:

(a) there was endemic goitre in the following areas as shown below:

	Okeiho	32%
	Tede	22%
	Sepeteri	12%
	Kishi	25%
	Shaki (Baptist High School)	13%
	Aha (Primary School)	24%
(i)	Ijeshaland	
	Ilashe	18%
	Esa-Oke	32%
	Imesi-Ile	23%
	Ifewara	22%
(iii)	Oshun	
	Igbeti	15%
	Ora	50%
(iv)	Ekiti	
	Orin	22%
	Oye	23%
	Osin-Ikole	35%
	Ikole	24%
	Araromi	37%
	Omuo	34%
(v)	Afenmai	
	Okpe	18%
	Ososo	15%
	Jettu	20%
	Iyereku	16%
	Afuda	16%

(*b*)   there was no endemic goitre in the following areas:

    (*i*)   Ibadan

            Akanran   2%

            Osegere   2.5%

            Lalupon   1.5%

            Moniya   2%

    (*ii*)   Ijebu

            Isonyin   2.5%

            Atan   3%

            Adowa   1%

            Ilishan   3.6%

            (Epe)   2%

    (*iii*) Remo

            Ogere   2.4%

            Ipara   5.8%

    (*iv*) Egba

            Osiele   3%

            Erin   1%

            Owode   2%

            Odeda   1.2%

    (*v*)   Egbado

            Igbogila   1%

             Ibeshe   1.6%

            Irogun   Nil

            Oke-Odan   2.6%

The survey revealed that endemic goitre, varying from 12% to 50%, was present in Oyo, Oshun, ljeshaland, Ekiti and Afenmai districts of South-Western Nigeria. Although goitre was present in Ibadan, Ijebu, Egba, Egbado and Remo districts but not high enough to constitute public health problems or to endemic degrees.

Thus there is a belt of endemic goitre which runs across the northern part of South-Western Nigeria (Fig. 12). This belt of endemic goitre coincides with a ridge of pre-Cambrian granite mountains which also runs across the northern parts of South-Western Nigeria. Figure 15 and Figure 16 show the typical scenery of these parts. The granite mountains skip the Niger and Benue River basins to become continuous with similar features north of Nsukka and Ogoja areas where endemic goitre has been described. Most of the rivers and small streams which supply the populations in the endemic areas originate from granite mountains. Figure 17 shows a stream originating from granite rocks in Osin-Ikole. Incidentally, this village is divided into two unequal parts by the motor road. The smaller part drew its water from this rock-hole
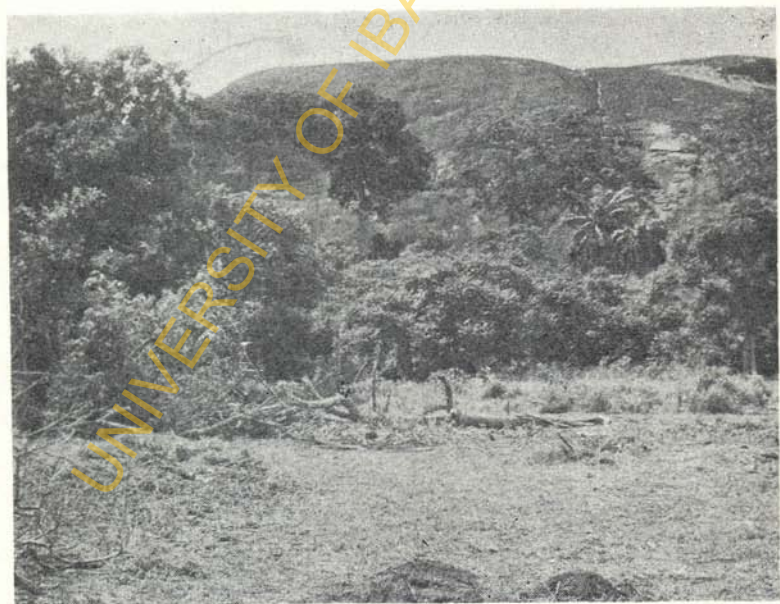

Fig. 15.   Scenery of mountainous rocks in Ijesha

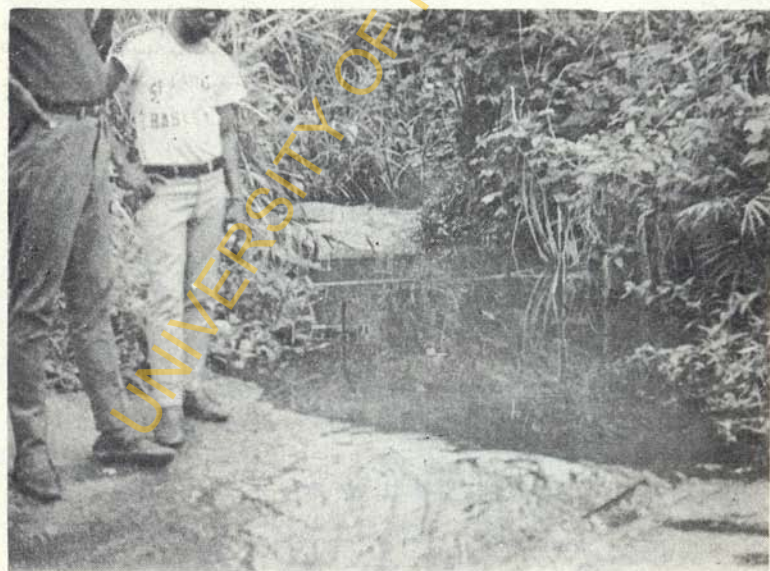Fig. 16. Scenery of mountainuos rocks in Ekiti

Fig. 17. A stream originating from granite rocks.

stream and the goitre incidence was 64%. The bigger part of the village drew its water from a stream a little way in the forest on their side and the goitre incidence was 22%. Figure 18 shows the source of a small river from the heart of a huge granite mountain. The river supplies water to a village with goitre incidence of 34%. The iodine content of water in the endemic areas varied between 0.4 to 2.6 ug/litre, whereas the iodine content of water from non-endemic areas varied from 5 to 20 ug/litre. The staple food in Oyo, Oshun, Ijeshaland, Ekiti and Afenmai areas was yam and its derivatives. Figure 19 shows a typical market scene in the areas of endemic areas where yam in various forms are sold. Figure 20 shows a mixture of pounded yam and something to wash it down with !
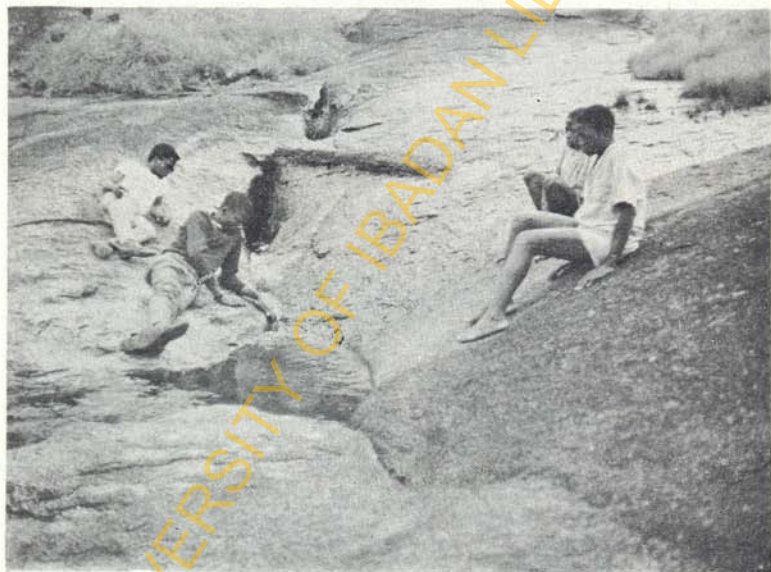

Fig. 18. Source of a stream from the heart of a rocky mountain.

Since these epidemiological investigations incriminated iodine deficiency as the main cause of simple endemic goitre in South-Western Nigeria, it was decided to study the pattern of iodine metabolism in these goitres. Here again I must acknowledge the co-operation and help I have enjoyed from the Heads and members of the Departments of Chemical Pathology, Morbid Anatomy and Radiology.

Fig. 19. *Market place scenery. Note the sliced dry yams exhibited for sale in a goitre endemic area.*
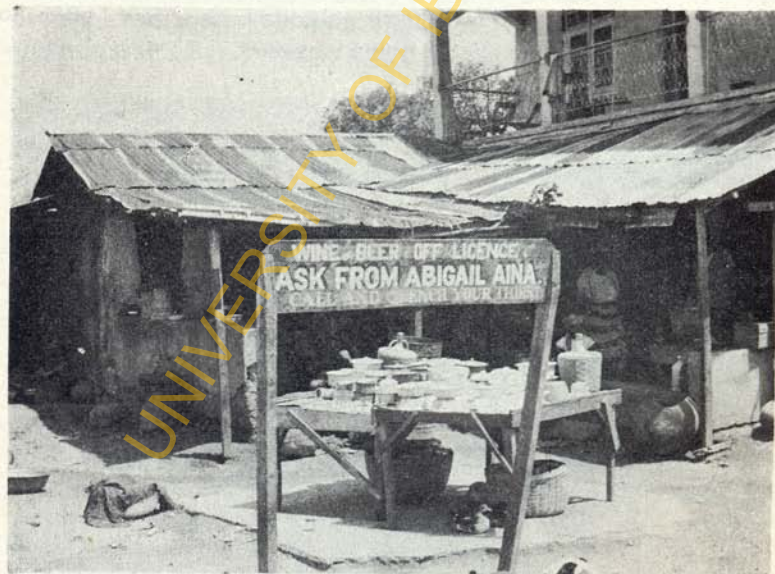

Fig. 20. *A local "Restaurant" where pounded yam is served. Beer and wine available to wash the food down!*

(*i*)   The radioiodine uptakes of the goitres were counted at six and 24 hours after ingestion of 50 to 120 uc. of radio-active iodine I^{131}. The simple endemic goitres almost invariably showed marked avidity for radioiodine. The uptake values obtained in a vast majority of them were as high as one would expect from hyperactive goitres. Indeed, the goitres were hungry for iodine!

(*ii*) Autoradiograms of the excised goitrous tissues were prepared as follows. Three to five days after ingestion of 50–120 uc. of I^{131}, the goitre was surgically removed, rapidly fixed, waxed and sectioned. The sections, 5–8 u thick, were placed against a radiological film in a cassette and kept in the dark for about 14 days. The films are then developed. The darkening of the films is an index of radioactivity of the section of the goitre, Figure 21 (*a & b*). The autoradiograms showed extensive incorporation of radioiodine into the goitres and thus further lend support to the finding of high I^{131} uptakes described above.

(*iii*) The intrathyroidal hormonogenesis was investigated by analysis of the thyroidal radioiodine labelled aminoacids. Three to five days after a goitrous patient had ingested 50–120 uc of I^{131}, the goitre was removed. Small portions
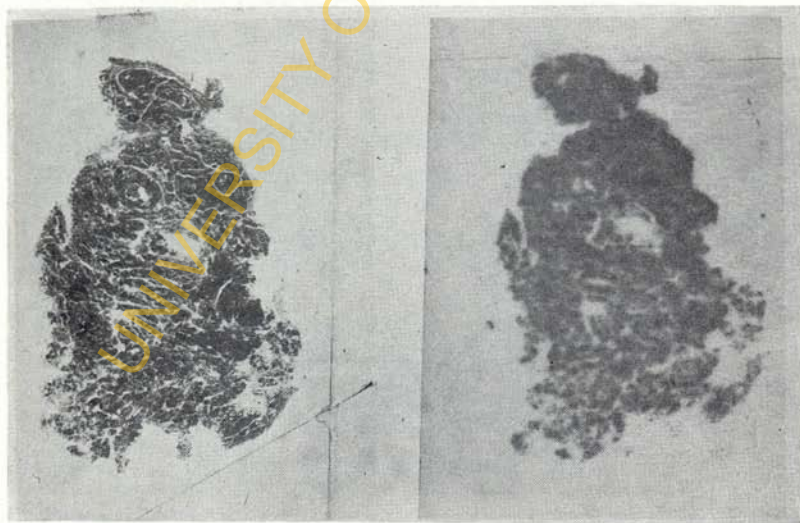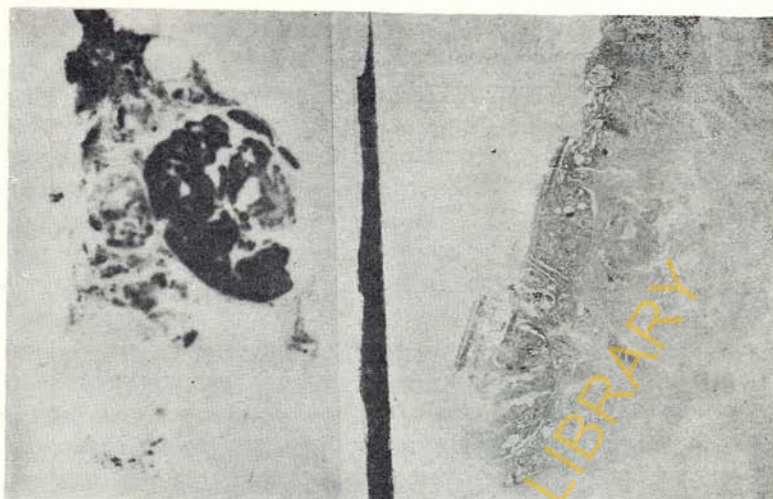

Fig. 21.   (a)   *An autoradiogram—showing diffuse incorporation of radioiodine.*

(b) *An autoradiogram showing intensive uptake of radioiodine in a nodule.*

of the goitre (40–50 gm) were immediately taken, homogenized and digested with trypsin through a complex biochemical process which time does not allow me to elaborate upon now. The extract of the digest was finally subjected to paper chromatographical analysis.

Figure 22 shows the chromatographic separation of the various thyroidal radioiodine labelled aminoacids. This analysis showed greater quantities of monoiodotyrosine (MIT) than di-iodotyrosine (DIT) with a higher than normal MIT/DIT ratio. This indicates a defect in the transference of iodine from MIT to DIT. There is also a marked decrease in tri-iodothyronine and, to less extent, in thyroxine formation. This pattern indicates marked slowing down of intrathyroidal hormone synthesis and modification of hormone secretion. However, the enlargement ensures that enough hormones are formed to keep the patients in euthyroid states.

Stanbury *et al.*,[19] postulated that such modification of hormonogenesis was related to iodine deficiency and this view was supported by Ermans[20] *et al.* The same type of hormone synthesis was induced in rats fed on iodine deficient diet by Leloup and Lechiver[21] and Querido *et al.*[22] Similar patterns of hormonogenesis were observed in human subjects living in iodine deficient goitre

endemic areas by Ermans.[23] Contrary-wise, Richards and Ingbar,[24] and Slingerland et al.,[25] found that high MIT/DIT ratio and low T3 occurred in the goitre of rats treated with propyl-thiouracil, a drug that interferes with hormone synthesis. These authors suggested that such modification of hormone synthesis was due to a goitrogen blocking action of iodination of thyroglobulin and inhibition of conversion of MIT to DIT. This finding raises the question of the possibility of a food goitrogen of the propylthiouracil type in the aetiopathogenesis of goitres in South-Western Nigeria.

The survey revealed that the most pervading staple food in the goitre endemic areas of South-western Nigeria was yam and its products whereas in the non-endemic areas the main food item was cassava and its products. It has, however, been shown that in some goitre endemic areas north of Nsukka unfermented cassava is consumed. Ekpechi[26] produced goitre in rats fed on unfermented cassava meals and postulated that the goitrogen in unfermented

Fig. 22. A chromatogram showing distribution of radioiodine labelled amino acids A typical picture of aminoacid distribution in endemic goitre.

cassava, the cynogenic glucoside (linamarin) either acted or was converted to a goitrogen of the thionamide group to act like the thiouracil goitrogen. But Delange and Ermans[27] found that ingestion of cassava meals in a highly goitre endemic region of Idjwi Island of Congo reduced the thyroid uptake of radioiodine I.[131] They disagreed with Ekpechi's postulate and argued instead that the goitrogenic effect of cassava was similar to that of thiocyanate which was also the catabolic product of cyanogenic glucoside, linamarin. The preliminary results of my investigations support the latter view.[28]

On the basis of the epidemiological findings and the pattern of intrathyroidal iodine metabolism of endemic goitre in South-Western Nigeria discussed above, it is concluded that iodine insufficiency plays a major role in the pathogenesis of endemic goitre in this region. It is significant to repeat that cassava and its products are less intensively consumed in the northern half of South-Western Nigeria where goitre IS endemic than in the southern half where goitre is NOT endemic. It is not, however, argued that iodine deficiency is solely the cause of endemic goitre in the affected areas since iodine deficiency has been known to play a permissive role in endemic goitrogenesis[29] but the permissive role appears to be decisive.

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