Nutrition Vol. 15, Nos. 11/12, 1999

Metabolic Maladaptation: Individual and Social Consequences of Medical Intervention in Correcting Endemic Hypothyroidism

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ABSTRACT

Endemic hypothyroidism has been studied in a Central African population in remote Congo (ex-Zaire) to investigate the prevalence, severity, causes, and potential control of this disorder, with questions as to why this disease is conserved, and whether it confers any adaptive advantage in this resource-constrained environment. Iodine deficiency, cassava goiterogens, and selenium deficiency were found to be the factors implicated in the severe hypothyroidism expressed in congenital cretinism and high goiter incidence in this isolated population, which continues to be under observation following medical intervention. Profound hypothyroidism was encountered in whole village populations as measured by serum thyrotropin determinations ranging from very high to over 1000 IU, and thyroxin levels ranging from low to undetectable; cretinism rates were as high as 11% and goiter incidence approached 100%. Assessment of endocrinologic status, caloric requirement, energy output, fertility, and ecologic factors was carried out before and during iodine repletion by depot injection. Hypothyroidism was corrected and cretinism eliminated in the treatment group, with goiters reduced in most instances (with regrowth exhibited in some who escaped control) and some symptomatic goiter patients were offered surgical treatment for respiratory obstruction. Individual patient benefits, including improved strength and increased energy output, were remarkable. The social and developmental consequences observed within the collective groups of treated patients were remarkable for an increase in caloric requirement and a dramatic increase in fertility that led to quantitative as well as qualitative increases in resource consumption. Micronutrient iodine repletion was not accompanied by any concomitant increase in macronutrient supply, and hunger and environmental degradation resulted. The highly prevalent disease of hypothyroidism is found in highest incidence in areas of greatest resource constraint. It may be that hypothyroidism is conserved in such areas because it may confer adaptive advantage in such marginal environments as an effect, as well as a cause, of underdevelopment. Hypothyroidism may limit energy requirements, fertility, and consumer population pressure in closed ecosystems that could otherwise be outstripped. Single factor intervention in a vertical health care program not sensitive to the fragile biologic balance and not part of a culture-sensitive development program might result in medical maladaptation. *Nutrition* 1999;15:908–932. ©Elsevier Science Inc. 1999

Key words: micronutrient repletion, medical maladaptation, vertical health care programs, conserved diseases, fertility and population pressures, endocrinologic adaptation response

INTRODUCTION

This paper deals with hypothyroidism in central Africa in an Azande population in Northeast Zaire. Hypothyroidism affects the individual victims of this disorder, as well as the collective society in which this metabolic deficiency has inhibited socioeconomic development. If this metabolic disorder is a disease affecting first individuals and secondarily the society that they compose, several questions arise: Why has this disorder arisen and been conserved within this population? Has hypothyroidism conferred advantages as well as disadvantages to the individuals and society affected? How will the control of hypothyroidism affect both individuals and their society?

The hypothesis to be explored is that the medical condition known as hypothyroidism is conserved in resource-poor environments. It has been, in fact, an adaptation to micronutrient and macronutrient insufficiency. Observations made in a longitudinal study of a population in an environment of iodine deficiency are analyzed before, during, and after intervention in treating hypothyroidism, and the effects in both individuals and their society are described regarding both the disorder and its treatment.

Comparative data are collected from a geographically nearby population—the Efe, often called "pygmies" in the literature[1]—who were studied similarly, but without the specific medical intervention program of iodine repletion, to serve as an external

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Nutrition 15:908–932, 1999

ELSEVIER

0899-9007/99/$20.00
PII S0899-9007(98)00123-3

control group for the treated Azande population. Data obtained before iodine treatment was initiated (an historic control) and from the group of Azande studied but not treated (concurrent control) were the comparisons within the Azande population serving as internal controls.

The study was carried out personally under the auspices of a mission station associated with Africa Inland Mission, but without major funding sources or sponsorship. Some volunteer labor was contributed through the World Medical Mission which, along with the study's volunteer participants, donated some of the supplies.

The initial population survey was undertaken with the belief that medical intervention to correct hypothyroidism might improve the well-being of those treated and result in collective social and cultural benefits from the relief of this biologic inhibition to development. Acting upon this mission objective, the medical relief effort has brought about expected medical and sociocultural benefits for individuals treated. There has also been a considerable unexpected impact of treatment on the population under observation following treatment. From the consequences—both positive and negative—of intervention in this sample population, conclusions are drawn regarding human adaptation to this resource-poor environment and the role of medical intervention to correct hypothyroidism as possibly being maladaptive in this environment of endemic hypothyroidism.

A corollary of the hypothesis is that medical intervention may have deleterious long term effects on the population's health if the malady treated has had adaptive advantage and has, therefore, been conserved within such a population.

HYPOTHYROIDISM IN THE ADULT AND CHILD

What Is Hypothyroidism?

Hypothyroidism is a disease characterized by decreased secretion of thyroid hormone resulting in subnormal regulation of metabolism. Its consequences are low energy output, obtunded mentation, and decreased caloric utilization. In the adult, compensatory goiter may develop in response to pituitary recognition of this subnormal metabolic state and appropriate increase of thyroid stimulating hormone (TSH). In the infant, the greater human tragedy of cretinism may ensue, which is failure of development in neurologic, stature, cardiovascular, and sensory faculties with retardation of all growth milestones and permanent developmental arrest.[2]

In terms of the individual, particularly at the stages of fetus, infant, and childhood, *development* refers to physical and functional growth and differentiation, so that stature, senses, strength, and learned psychosocial capabilities are able to proceed in the growth pattern characterized by growth milestones (e.g., age norms for height, weight, weaning when individual first begins to sit up, walk, talk, etc.). Hypothyroidism is a condition that retards these development processes and in severe cases permanently stops them. In terms of a society, *development* refers to the socioeconomic complexity and productivity characterized by appearance and differentiation of specialized social institutions, literacy, gross domestic product, and consumption and processing of resources. Hypothyroidism has its highest global incidence in populations described as lesser developed in these socioeconomic conditions. The consequences of hypothyroidism make it understandably classified as a disease with quite apparent implications for retarded development of both individuals and the culture of the society affected.

Hypothyroidism can be studied by measuring hormones in the blood (thyroid hormones would be low, thyroid stimulating hormone would be elevated), presence and degree of goiter and cretinism, and metabolic rate estimation through calorie consumption. As goiter and cretinism are terms describing hypothyroidism in the adult and child, respectively, these terms are defined here, since each may be assessed in the field without reliance on laboratory analyses of hormone assays, the results of which are often determined and reported much later.

Goiter is defined as an enlarged thyroid gland, a swelling in the anterior inferior part of the neck that may be palpable (typically when the size exceeds twice the adult median thyroid gland size of 18.0 g), visible (typically when the size exceeds four times the adult median thyroid gland size, or around 75.0–100.0 g), and sometimes massive, occasionally grossly distorting the anatomic configuration of the head, neck, and chest (in some instances exceeding a kilogram and approximating the size of the patient's head). Goiter may cause problems for the individual who bears it ranging from disfigurement, discomfort, coughing, and difficulty swallowing to obstruction of breathing, a life-threatening complication.

Cretinism is defined as congenital hypothyroidism and has even more significant consequences than goiter in human development. As will be described in a proceeding section, cretinism represents the retarded or arrested intra-uterine development of an infant born with significant impairment ranging from retarded growth and developmental milestones to stillbirth from insufficient energy utilization and suppressed metabolic development.

What Causes Hypothyroidism?

The majority of the causes of hypothyroidism are known, and most are readily correctable. The most prominent cause in Africa and many other areas is iodine deficiency. Iodine is an inexpensive dietary trace element that could be made available, and should be capable of repletion in those who are deprived of it due to their geographic remoteness from sources of this trace element.[3] Lesser common causes of hypothyroidism in some societies are substances known as goitrogens. These factors are substances that prevent organification of iodine into thyroxin. The effect of some of these goitrogens, for example, thiocyanates, can be mitigated by either avoiding the dietary vegetable products that contain these thiocyanates through a shift of dietary starch staples or a change in the way some foodstuffs are prepared to reduce goitrogen content.[4] A third cause of hypothyroidism among those factors known or suspected includes dietary deficiency of cofactors necessary for reduction of iodide, including a trace element antioxidant, selenium, either present in a varied balanced diet or capable of fortification, as with iodine, in a dietary supplement.[5]

Where Is Hypothyroidism Found and Why?

Geographic features that correlate with regional iodine deficiency include soils of volcanic origin with low iodine (e.g., some Indonesian Islands),[6,7] soils leached of iodine by glacial action (e.g., Great Lakes, Alpine central Europe, Andes, the Himalayas), or soils leached by periodic inundation and elution of water-soluble nutrients (e.g., equatorial and tropical rain forests). In the ex-Zaïre (now renamed the Democratic Republic of the Congo) study area, the combination of lava substrate and cyclic inundation (leaching) is an explanation for the iodine-poor environment.[8] Additionally, this remote Central African location is far removed from natural sources such as iodine-rich seafoods or commercially fortified products such as iodized salt.

The extent of hypothyroidism is a serious global public health problem.[9] Nearly a billion people, or one-fifth of the planet's inhabitants, are affected—the majority of them have marginal deficiency that inhibits their reaching their full potential (75%), but many manifest hypothyroidism through goiter (20%, or a number approaching the size of the US population) and a tragic amount (3.5 million) exhibit and suffer a permanent preventable retardation.[10] In fact, iodine has been called the "mind-protector."[11] The populations affected by hypothyroidism are among the poorest on the globe. They are distributed in those tropical, mountainous, or volcanic regions that are least developed with populations with the least potential for developing the resources of these environments.[12,13] These foci of geologically induced goiters[14] are places where geologic features allow prediction of probable hypothyroidism; in the world today, these areas are found nearly uniformly to be lesser developed regions of the world. This disadvantage is based at least in part on the lack of energy, ambition, and resourcefulness that are characteristic of the hypometabolism of hypothyroidism, sapping the human resources, whatever the limited potential of the natural resource environment.[15–17]

The World Health Assembly has recognized this coincidence of iodine deficiency disease in the under-developed regions of the world and at its 43rd assembly in May, 1990 established the goal of elimination of iodine deficiency disease by the year 2000.[3] An organization entitled the ICCIDD (International Council for the Control of Iodine Deficiency Disorders) has been working toward the achievement of this global goal, now nearly approaching the deadline of the timetable for its accomplishment.

Consequences of Hypothyroidism

The consequences of hypothyroidism are severe. The causes are known and correctable, so why is it that this disease has persisted? It seems by some coincidence that it most severely affects the poorest of the world's populations in the areas that are most resource-depleted, and this fact leads to the question of whether this association is one of cause or effect. It is true that poverty and hypothyroidism appear congruent on the world's map of geographic medicine. If the disease of hypothyroidism is maladaptive, why has it been conserved? And, particularly since the modern advent of global health programs for prevention of serious disease, why cannot this disorder be eradicated? Since such a goal has been stated and acted upon with a timetable set for elimination of hypothyroidism, what are the likely possibilities that this goal will be successful, and what are the probable consequences if it should succeed or fail?

How Can Hypothyroidism Be Studied?

Before any understanding of how deficiencies in the environment and human disorders may be related, the best approach is to define, describe, and measure aspects of the environment and the affected society before evaluating the role of one isolated factor such as iodine in human growth and potential. Understanding how much deficit is due to the identified micronutrient, and how intervention in this factor by repletion might change both individuals and the society composed of those individuals, might come later with a cumulative assessment of the changes in form and function.

From the perspective of my interest in the biological, environmental, and cultural adaptations of remote populations and with a professional background in surgical endocrinology, I had sought out the most significant endemias of hypothyroidism to attempt to address the questions of the endemias' characterization, why hypothyroidism is conserved, and the individual and social consequences of hypothyroidism and its correction. One of the most severe endemias so far recorded on earth is the study region of this investigation in Central Africa. The area selected for this study of endemic hypothyroidism is in the upper reaches of what was called "Bas-Uele," first recognized by colonial district officers when this area was "Congo Belge" and then reported by several Belgian investigators through preliminary surveys.[18]

When an isolated factor in this region is selected as the independent variable in a study of a population, it is possible that other events in the environment may be changing as well, i.e., the factor cannot be completely isolated. To identify as completely as possible covariables and to the degree possible examine untreated controls within the study population adds strength to the associations depending on the independent variable—in this instance, the micronutrient, iodine.

If observations made in a population are compared with reported historic data in the same population, there is no control for the cofactors that may be brought in with the independent variable. A parallel social group in the same region and an internal untreated control group within the same population studied contemporaneously constitute a better control for these unknown cofactors' confounding influence. The same investigators observed different ethnic groups in a different geographic area in the population survey. In these other populations, the micronutrient iodine was not repleted, even though other medical intervention was introduced for services to the control population. This second population was compared with the study group under longitudinal surveillance.

Where Was This Study Conducted?

This study was conducted in an Azande population through the longitudinal study of profoundly iodine deficient populations in the Uele region of northeast Congo (at the time designated Zaire). This region, defined as Sasaland (because of the hereditary chieftainship of the region bearing the Azande family name Sasa), is in a remote part of Central Africa (Fig. 1) in which little study or intervention had previously been carried out or reported.

In this region, endemic hypothyroidism is both highly prevalent and profound in its consequences on the juvenile and adult members of this affected community. This society and its members are as severely affected as any group on earth according to the standards of the ICCIDD and might, therefore, be significant beneficiaries of The World Health Assembly resolution at the 43rd assembly in May, 1990 to eliminate iodine deficiency disease by the year 2000. Before implementation of this goal, however, a survey of a very significant endemia such as that described in this Uele region under study in the Congo could assess not only the impact of the disorder within the population, but also what might be expected to result from successful intervention in treating this disorder.

Micronutrient repletions might not be the only thing going on in the society during the period of this observation. But some estimation can be made as to whether the disease, or its treatment by iodine repletion alone, unmitigated by any other introduction of micronutrient or macronutrient supplementation, might be maladaptive while noting any other concurrent programs in other micronutrient enrichment, macronutrient expansion, and general development assistance. In addition to iodine repletion, the raising of the metabolic rate by iodine correction of hypothyroidism might be mitigated by an increase in caloric intake concomitant with iodine administration.

In some isolated societies, such as a few of those represented in Central Africa, the Equatorial rain forest is an environment in which water, fuel energy, and calorie-dilute food stock are adequate and accessible, yet human energy resources are relatively less well developed. This has led these cultures to subsist on what can be extracted or produced locally without a good deal of their consumption being based on trade goods that might be brought in from elsewhere, since few exportable unique resources are available in these environments.

Extricative industry is very limited since the forest does not recover after timbering, no pasturing or agronomy is productive because of poor soil and abundant predators, mineral resources are absent compared with the wealthier "Copper Belt" region elsewhere in Zaire in the Kasai Province, and fruits, rubber, or other exotica have not thrived when introduction was attempted.

There are only two native substances in the environment for

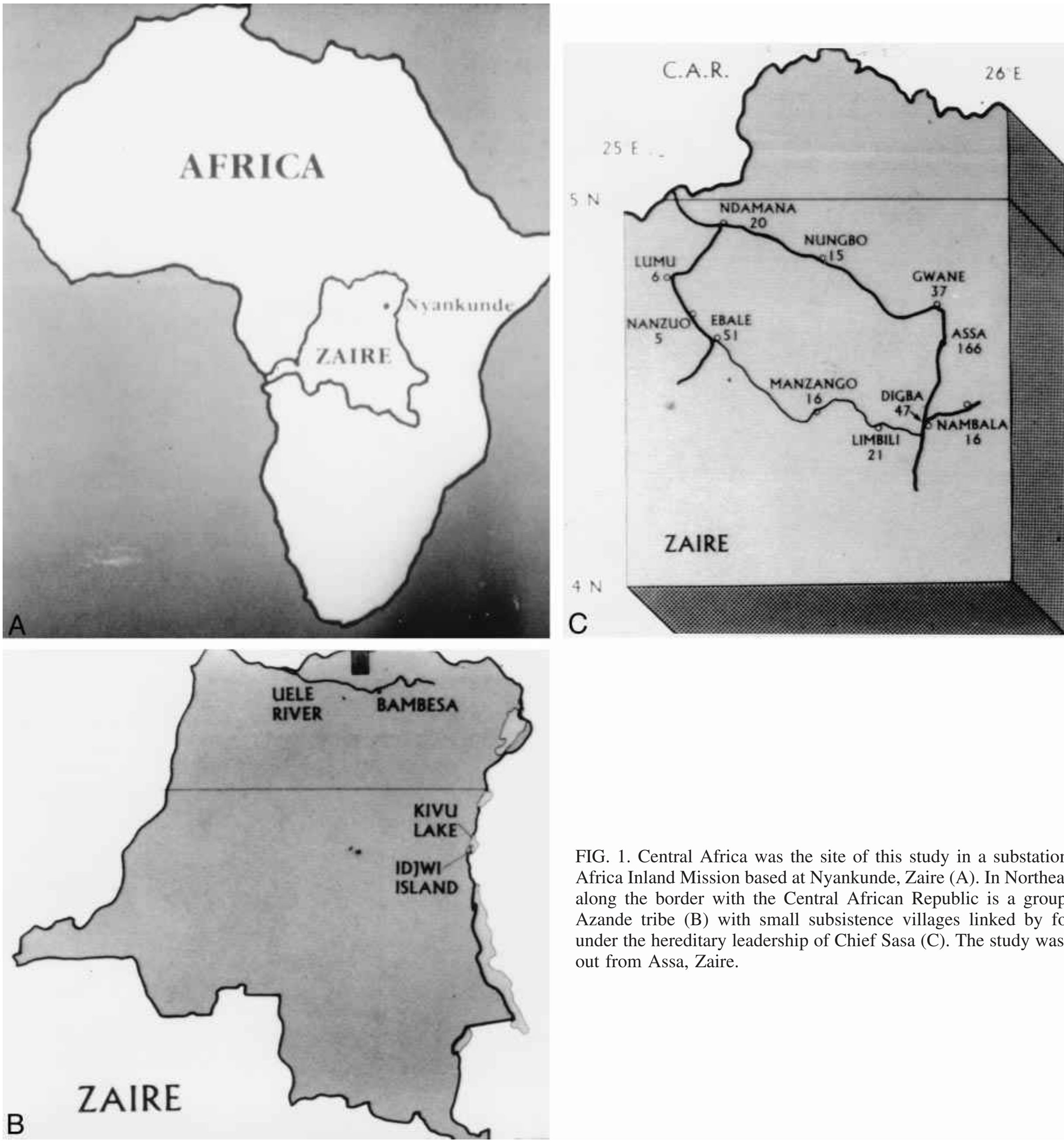

FIG. 1. Central Africa was the site of this study in a substation of the Africa Inland Mission based at Nyankunde, Zaire (A). In Northeast Zaire along the border with the Central African Republic is a group of the Azande tribe (B) with small subsistence villages linked by footpaths under the hereditary leadership of Chief Sasa (C). The study was carried out from Assa, Zaire.

which a world market exists—one animal and one vegetable, extracted from the root of an indigenous tree. The first is "White Gold," the ivory from elephant poaching that has been the highest value added industry, and the second is rauwolfia, the root extract formerly used to produce antihypertensives. The international pressures to devalue the ivory trade had resulted in increased intensity of poaching younger bulls and elephant cows to keep up with the falling prices as the herd was decimated; rauwolfia has been preempted by newer generations of synthetic antihypertensives and rauwolfia harvesting is now obsolete. The collapse of these two external markets has returned the population to the subsistence that has always been its mainstay, with the very rare export of the only remaining forest product, palm oil, inadequate to maintain trade routes through which it can be transported.

This pattern of subsistence, particularly if marginal, has favored less complex societies that appear to be less economically developed by Western standards. This under development could result from deficiencies in natural resources or in human capital and energy resources whether internal or external to the society.

Hypothyroidism is a fundamental metabolic cause of decreased human energy utilization, and may constitute one of the chief inhibitions to development.[19] Its role in underdevelopment should be understood before applications of concurrent development programs are initiated in environments where this disorder is endemic. A motivation for understanding iodine deficiency disorders is the tragic loss of human potential for development in populations that are severely affected.

The region under discussion is in equatorial central Africa (see Fig. 1A) in a region subserved by an Africa Inland Mission (AIM) station based in Nyankunde. As noted in Figure 1B, the region

TABLE I.

GOITER DISTRIBUTION AMONG ADJACENT POPULATIONS OF EFE AND LESE TO COMPARE WITH AZANDE GROUPS

	Goiter	0	Ia	Ib	II	III	Total
Efe	Female	42	2	1	1	0	46
	Male	41	1	0	0	0	42
	Total	83	3	1	1	0	88
Lese	Female	68	12	8	27	10	125
	Male	69	1	1	9	3	83
	Total	137	13	9	36	13	208
Others	Female	21	4	1	7	3	36
	Male	27	4	2	8	1	42
	Total	48	8	3	15	4	78

Goiter incidence among tribes was: Lese 34.1%; immigrant members 38.5%; Efe 5.7%. There is significant difference between the Efe and Lese (chi-square = 72.26, $P < 0.001$) and also between Efe and the others (chi-square = 48.90, $P < 0.001$). There is not significant difference between the Lese and the others (chi-square = 0.45, $P > 0.01$). Goiter incidence among women examined: Lese 45.6%; immigrant members 41.7%; Efe 8.7%.

along the northeast border adjoining the Central African Republic in the drainage of the Uele tributaries is at some remove from other Zairian endemias previously well described such as those near Lake Kivu on the other side of the equator.[20]

The subprefecture in which the study was carried out is among the group of Azande headed by the hereditary Chief Sasa in a part of Zandeland referred to as Sasaland. This is an area of volcanic rocky savanna adjacent to small riverine tributaries of the Uele that are far removed from any major navigable river or road transportation. In this region, subsistence farmers engage in hunter-gatherer activities from village settlements connected by footpaths (Fig. 1C).

The Zande culture has been the subject of many studies, including the classic works of Evans-Pritchard.[21] The Azande are a Nilotic people that migrated down from the Sudan in the pre-European colonial period and subdued the population of Bantu peoples that had migrated into this region some unknown number of generations before. The Azande were considered resident throughout all historic periods.[21]

The local Bantu are represented principally by the Basili, who had intermarried with the ruling overlords of Azande chiefdom. The original Azande conquerors set up a dynastic dominance while intermarrying with the indigenous Bantu peoples they had conquered. The royal bloodline has been successively diluted over 10 generations within the hereditary rulers of the region, but the culture and language dominance of Azande has expanded under their semiautonomous administration in contemporary Congo (ex-Zaire.) The majority of the population is primarily of Bantu origin and phenotype, although the royal family is still distinctive in these respects. With this mixture of genes that are predominantly Bantu and a ruling culture that is predominantly Azande, Zandeland encompasses an estimated population of 2 million scattered in isolated groups throughout northern Congo (ex-Zaire),[22] the Central African Republic, and the Sudan. An estimated census of the Azande in the subprefecture under the rule of chief Sasa, estimated by the chief himself, is that 40 000 subjects inhabit the region of Sasaland in which the study was carried out.

Another population, the so-called Pygmies of the Ituri forest, with which this group of Azande have little contact, have been sampled as a comparison. This comparison population is of different genetic and cultural background, but has been resident for a prolonged period of time in a geographically contiguous environment based in similar volcanic geology, and subject to the same periodic cycles of wet and dry seasons of the equatorial rain forest.[23] Medical care was brought to these populations from the same AIM base from Nyankunde, but without a population-wide medical intervention program in hypothyroidism.[24] Measurements were carried out in this distinctive group as a control. Measurements made among the Efe and Lese, collaborating hunter-gatherers and agriculturalists, respectively, in pygmy societies, included incidence of goiter (Table I) levels of thyroid hormones T_4 and T_3 as well as TSH and urinary iodine excretion (Table II) and correlation of goiter and fertility (Table III).[25]

The soil of the region under study is very poor in both organic content and several measured micronutrients. The results of the soil analysis[26] demonstrated that the selenium available showed less than half the minimum adult requirement, roughly equivalent to similar reports of selenium soil deficiencies in the great basin of China where selenium deficiency disease was first reported in its greatest incidence.[5] Principal among the micronutrient deficiencies are iodine, iron, and selenium.[27] As is true in most equatorial ecosystems, the vast majority of organic material and the recycling of it in the structure of food chains within the canopy takes place above ground level, and depends very little on nutrient absorption from the thin volcanic rocky soil exposed to periodic cycles of inundation and desiccation.

The staple diet of this population includes principally root crops, predominantly cassava. This staple, which can be stored year-round as a dried woody root, is varied with foraged forest products, peanuts, plantains, and occasional supplementation from animal fats and proteins from hunting.

Samples of the food stock brought to the local market for barter were obtained (Fig. 2A) and analyzed for iodine content, which was uniformly low, as was that found in the rather scarce quantities of local salt (Fig. 2B). The principal caloric intake consists of a once-a-day evening meal of pounded cassava root prepared after soaking it in a stagnant pool to soften the pulpy root. This bulk diet is rich in fiber and poor in calories and vitamins. One of the principal vitamin deficiencies is vitamin A, and when combined with the micronutrient deficiencies in iron, iodine, and selenium, the *total* macronutrient protein-energy is of marginal adequacy. To define caloric balance as stable weight on a given protein-energy intake, an approximate calorie count was carried out on a group of adults and children estimating the proteins and caloric content of the energy-dilute food stock, based mainly in cassava meal. This caloric survey showed some adults to be in caloric balance at around 800.0–1000.0 calories per daily intake,

TABLE II.

THYROID FUNCTION TESTS AND IODINE EXCRETION IN URINE IN DIFFERENT POPULATIONS OF ADJACENT ZAIRIAN RESIDENTS

Parameter	Unit of measure	Efe	Lese	Others
T_4	μg/dL	12.1 (5.6) $n = 5$	11.4 (2.0) $n = 16$	10.3 (2.0) $n = 19$
T_3	ng/dL	224.0 (81)	179.0 (24)	174.0 (47)
TSH	mU/L	4.1 (0.8)	2.1 (1.4)	1.8 (0.7)
UIE	μg/L	40.5 (13.4) $n = 2$	22.8 (14.7) $n = 9$	33.5 (29.9) $n = 11$
IGF-1	ng/mL	61.1 (43.0) $n = 26$	152.8 (65.9) $n = 10$	127.8 (62.4) $n = 9$

By Pearson correlation testing, tribe correlates significantly with TSH ($P < 0.01$) and IGF-1 ($P < 0.001$): TSH, E versus L ($P = 0.022$); E versus O ($P = 0.057$); L versus O ($P = 0.548$). IGF-1, E versus L ($P = < 0.001$); E versus O ($P = 0.001$); L versus O ($P = 0.409$). No significant tribe correlation exists with T_4, T_3 and UIE: T_4, E versus L ($P = 0.8$); E versus O ($P = 0.523$); L versus O ($P = 0.116$). T_3, E versus L ($P = 0.291$); E versus O ($P = 0.251$); L versus O ($P = 0.676$). UIE, E versus L ($P = 0.153$); E versus O ($P = 0.629$); L versus O ($P = 0.310$).
IGF-1, insulin-like growth factor-1; Mean (Standard Deviation); T_4, T_3, thyroid status; TSH, thyroid stimulating hormone; UIE, urinary iodine excretion.

whereas children were suffering significant malnutrition from marginal caloric intake.

In addition to the few micronutrients supplied by the cassava, there is the problem of a toxic component as well since a goitrogen, cyanide, is present in the cassava. This does not so much cause as exacerbate the iodine deficiency from the environmental scarcity of iodine. The preparation method of the cassava is important since, particularly in the dry season, it is soaked in pits that have an increasing cyanide content over the season. Running streams that might be preferable for preparation are not always available, and might cause the loss of some of the food stock if it escaped downstream during soaking. Assays of water, soil, and food stocks along with local salt (when available) have shown profound iodine deficiency, as well as an increase in cyanide content in the preparation of the cassava when soaked in stagnant pits (Fig. 3).

TABLE III.

PREVALENCE OF STERILITY AND GOITER IN NORTHEAST ZAIRE

	Bas-Uele (%)	Haut-Uele (%)	Ituri Forest (%)	Nyankunde (%)
People examined	522	412	83	84
Primary sterility	125 (23.9)	51 (12.4)	12 (14.5)	4 (4.8)
Secondary sterility	150 (28.7)	27 (6.6)	2 (2.4)	14 (6.6)
Incidence of goiter in female population (%)	83.3	73.2	55.4	12.5
	$n = 1127$	$n = 621$	$n = 195$	$n = 168$

FIG. 2. Samples of the few items of food stock available for barter at the local market (A) were analyzed and found to have uniformly low iodine content; this was also true for the scarce quantities of local salt (B) that were tested.

To be synthesized into thyroid hormone, elemental iodine must first be taken up in the body and reduced to iodide, the form in which iodine can be incorporated into thyronine. This preliminary process in thyroid hormone synthesis is referred to as organification of elemental iodine and is necessary for thyroid hormone

FIG. 3. Cassava preparation begins with soaking the root in a pit of water before pounding the woody pulp to flour; over the season, cyanide concentration increases in the soaking preparation.

production. When enriched in the cassava soaking process and ingested, the cyanide is metabolized to thiocyanate in the body, a compound that blocks organification of iodine, exacerbating the relative iodine deficiency by blocking the thyroid's ability to synthesize thyroid hormone in a dose-dependent fashion. Both iodine concentration and cyanide concentration are dose-dependent in their effect—the iodine in thyroid hormone synthesis and the cyanide in the toxicity that impedes this synthesis. In fact, thiocyanate is the product used medically to block overactivity of the thyroid gland; however, dietary intake of even enriched cyanide content would not get to the levels of thiocyanate employed therapeutically to treat hyperthyroidism.[28]

Cassava is a New World product, and probably arrived in this area not long before or with the Azande migration. Cyanide content of cassava is not unique to this root crop, but its concentration in this species is higher. Exclusive or dominant intake of this calorie source would accentuate the problem of iodine deficiency but not create it. Those who are more affluent in this society and who may depend less on cassava as a principle intake (for example, the ruling Azande families) still are not free of goiter or cretinism and, in fact, Chief Sasa himself and the ancestral portraits of the ruling chiefs before him exhibit very prominent displays of goiter.

The Chief's half-brother, also bearing the royal name Sasa, is shown with the author in Figure 4A. He is of comparable age, but exhibits stunted stature, lumbar bordosis, splayed stance, clumsy gait, and the other features of congenital hypothyroidism (Fig. 4B). He is deaf-mute, retarded in intelligence, and capable of limited self-care. His TSH is 718.0 IU/mL, T_4 0.2, and T_3 16.0; for comparison, those values for the author serving as a control are: TSH 3.7 (Nl: 0.5–4.0 uIU/mL), T_4 6.21 (Nl: 4.00–11.00 μg/mL), T_3 125.7 (Nl: 70.0–220.0 ng/dL).

Hypothyroidism in the Uele endemia is due to iodine deficiency. This iodine deficiency effects newborns severely in congenital cretinism, and adults with acquired goiter through the compensatory mechanisms of the pituitary's TSH stimulation of the thyroid gland hypertrophy. Despite compensatory efforts, the iodine-deficient population remains hypothyroid, and even marginal iodine deficiency is made worse by the cyanide content in the principle staple source of calories, the cassava that also acts as a goitrogen compounding the effects of iodine deprivation.

HYPOTHYROIDISM—A METABOLIC DISEASE

The effect of hypothyroidism is reflected differently in the adult or child, and this clinical difference will be investigated in this area of very high endemic affliction of both age groups.

In the human adult, hypothyroidism is characterized by low energy output, inactivity, and subnormal metabolism. The thyroid itself undergoes compensatory hypertrophy into a goiter, an enlarged thyroid gland, sometimes enormously expanded with grotesque disfiguration of the throat and neck. The development of a goiter is a compensatory mechanism. In response to the effects of severe iodine deficiency, the pituitary gland secretes excess TSH, which partially mitigates the effects of the deficiency. Goiter may also result from other concomitant stimuli that are called goitrogens, most of which act through similar mechanisms by making what little iodine is available less so. Some goitrogens exacerbate iodine deficiency that might otherwise be compensated for by the mitigating hypertrophy of the thyroid gland.[29]

If there is a marginal iodine supply taken in from the environment, and the thyroid is unable to synthesize enough thyroid hormone from the rate-limiting deficiency in iodine, pituitary response to this hypothyroidism may make possible enough TSH-stimulated hypertrophy in the now goitrous thyroid gland to trap and organify more of the minimally present iodine to bring the patient's thyroid hormone secretion closer toward euthyroid normal status. Goiter, therefore, is a compensatory response to the pituitary stimulation that mitigates hypothyroidism. Circulating thyroid hormone is brought closer to normal by means of the extra secretion of this anatomically abnormal goitrous hypertrophy. Though this compensatory goiter might approach normalcy from hypothyroidism, it never can achieve normal metabolism, since to do so would quench the pituitary TSH stimulation that brought about the thyroid overgrowth. Further, the other substances referred to as goitrogens can interfere with iodine uptake and incorporation in thyroid hormone, making a relative iodine deficiency profound, despite TSH-mediated pituitary compensatory efforts. Some types of goitrogens may also directly stimulate the thyroid gland to hypertrophy.

Despite the enlarged thyroid gland, therefore, thyroid hormone production never rises to normal in these individuals who have failed in this compensatory effort, as reflected both by measure of their low thyroid hormone in circulation and the increased TSH hormone levels—both of which define hypothyroidism based on the laboratory definition of diagnostic criteria. Figure 5 illustrates this obvious consequence of iodine deficiency in the adult in the formation of a goiter.

Through the simple means of clinical staging of goiter development by gross observation promulgated by the World Health Organization (WHO) (Table IV), the goiter that is obvious in the patient in Figure 5 would be classified as a "WHO Class III."

FIG. 4. Sasa, half-brother of Chief Sasa, is depicted with the author (A) for comparison of stature and morphologic features, with thyroid hormone and thyroid stimulating hormone values compared within the text. Although deaf/mute, he is capable of communicating by writing his wishes (B) in the sand.

FIG. 5. Goiter is an acquired response to iodine deficiency representing the thyroid hypertrophy in response to stimulation by thyroid stimulating hormone as a compensatory mitigation of hypothyroidism; the goiter that results may reach grotesque size and disfigurement (as seen here in a World Health Organization Class III goiter; see Table IV) and may cause dangerous airway compression.

Despite the goiter—the attempt on the part of the much enlarged thyroid gland to trap as much as possible of the sparse iodine that the environment can deliver—this patient and most others in any area of severe iodine deficiency will still be hypothyroid. This is manifest by their low energy utilization in clinical estimation of hypothyroidism and the measurements that can be made in such individuals of the decreased thyroid hormone and much increased TSH. These levels reflect attempts, even if inadequate, of this compensation. Goiter, therefore, is an adult manifestation of iodine deficiency, and the hypothyroidism that is still demonstrable reflects the inadequacy of even the hypertrophied gland to overcome this environmental micronutrient insufficiency.

In children, congenital hypothyroidism has far more profound consequences, including the arrested or retarded development potential qualitatively described as cretinism. Far from reaching their full potential in normal childhood development, cretins may assume the appearance of a protracted infantilism for lack of physical—and particularly mental—development. Cretinism and care of affected individuals imposes an additional burden on the often scarce resources of the Third World settings in which iodine deficiency, goiter, and cretinism are endemic.[30]

Cretinism may take two principal forms, either through the predominant manifestation of the "neurologic cretin" or the "myxedematous" form. The neurologic cretin is usually retarded, sometimes profoundly, often is deaf, has stunted stature and growth, has unusual gait and station, and reflex responsiveness.[31] Myxedematous cretins often express the impairment by additional manifestations of puffy edema collections and cardiac congestive failure. As seen in Figure 6, there may be some mixed congenital manifestations of both forms in some cretins. For reasons that are unknown, the proportion of neurologic to myxedematous cretins is quite different in different geologic locales. The vast majority of cretins in the Assa area are of the myxedematous form, the reverse of the situation in Karawa, another region of severe hypothyroidism endemia in Zaire 1000 km distant from the region under study.[22]

Some cretins exhibit a vacant, unblinking glazed affect, and fail to accommodate to glabellar taps ("blinks" that a normal individual would erase in tachyphylaxis). Some have characteristic gaping open-mouthed facies with protruding tongue, splayed feet, broad-based stance, exaggerated lumbar lordosis, nape kyphosis, and stunted broad digits (Fig. 7). Characteristic cutaneous patterns on digits and palms are dermatoglyphic markers of endemic cretinism.[32] Development milestones are inappropriately delayed for chronologic age, as can be seen for retained primary teeth even while secondary teeth have erupted (Fig. 8) and delayed sexual maturation in which ovulation may begin sometimes after 30 y (Fig. 9).

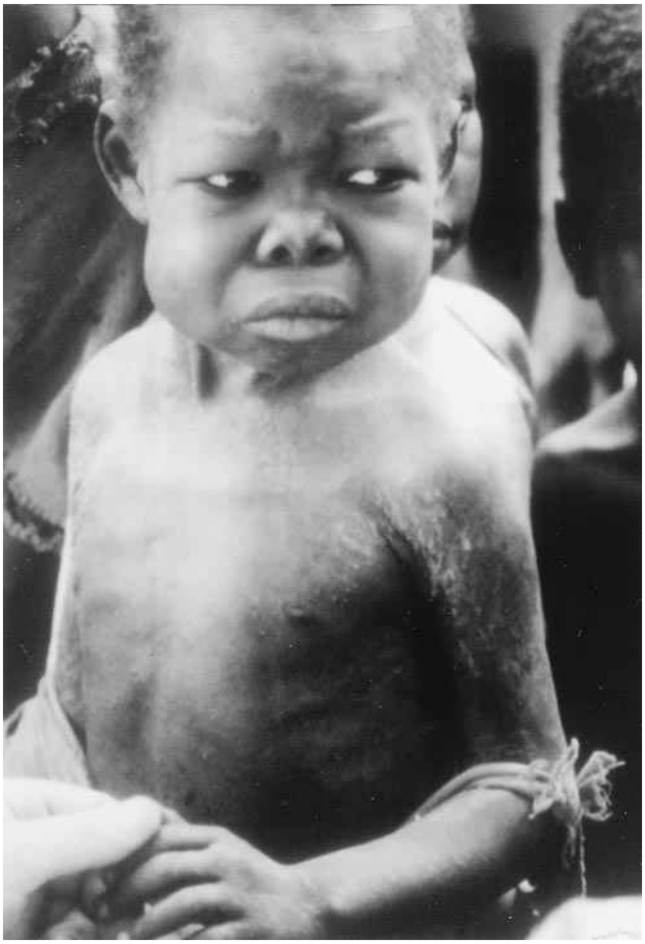

FIG. 6. Cretinism may assume both neurologic and myxedematous forms in some affected individuals, as seen in this portrait of Third World misery.

HOW WAS THIS STUDY CONDUCTED? MEASUREMENTS AND MORPHOLOGY APPLIED IN ENDEMIC HYPOTHYROIDISM

The methods of the population survey and random selection of the intervention arm of the hypothyroidism study began with a population of 400 patients studied from 1984–87, expanded to 700 patients under observation from 1987–90, and carried forward from 1990 to the present, following the investigators leaving the field after 4000 patients were treated (representing 10% of the population of the Sasaland subprefecture).

Random selection of patients first entered into the study was controlled for representative age distribution, and equal representation of village and forest habitation along with balanced sex distribution.

Goiter measurement in the population surveyed is by clinical classification according to the WHO scale. Beyond the WHO classification in rapid assessment through the scheme listed in Table IV, well-practiced clinicians examined each individual patient and estimated in grams the size of the goiter present at the time of examination. Repeated assessment of 400 and more patients not only sharpened the precision of this estimation, but these same clinicians also had the benefit of the next, more accurate, goiter measurement—the weight of the excised specimen estimated earlier—on a gram scale after removal. This clinical estimation (Fig. 10A) is combined with photography done in front and profile views against a metric grid (Fig. 10B) to support the clinical estimation when confirming the serial observations.

The most ingenious of the goiter measurements to be adapted in this low technology setting of observations in field study involves goiter perimetry by tracing. A sheet of tissue paper is applied to the contours of the hyperextended neck (Fig. 11A) and an outline of the palpable limits of the goiter is traced. This tracing is stored in the patient's record, and is also digitized by a calibrated perimetry wheel (Fig. 11B). The images of the traced goiter are compared at intervals along with changes in the perimeter recorded, clinical estimations, and, photographic evidence (Table V).

TABLE IV.

WHO GOITER CLASSIFICATION

0	No goiter
I	Palpable, not visible
II	Visible with neck extended
III	Visible with neck flexed; massive

Further measurable observations may be made of the adults and the children in an affected population that reflect iodine deficiency and hypothyroidism as well as a baseline characterization of the people in whom it occurs. Measurements obtained in the study of individuals affected include the anthropometry, height (Fig. 12), weight, age, vital signs, and neurologic determinations including reflexes and grip strength. Further determinations are made to assess goiter in both presence and size and any change over the time of the longitudinal study. Blood and urine samples are collected for assessment of hypothyroidism in an assay of the level of thyroid hormone, TSH, as well as nutrient elements such as iodine, selenium, and thiocyanate.

In addition to these morphologic measurements, serum assays were carried out on blood drawn from each of the subjects entered into the study. The blood was hand centrifuged and refrigerated by solar powered vaccine refrigerator until frozen by kerosene freezer for later sample determination. These measurements included iodine, thyroid hormones (T_4 and T_3), and TSH by radioimmu-

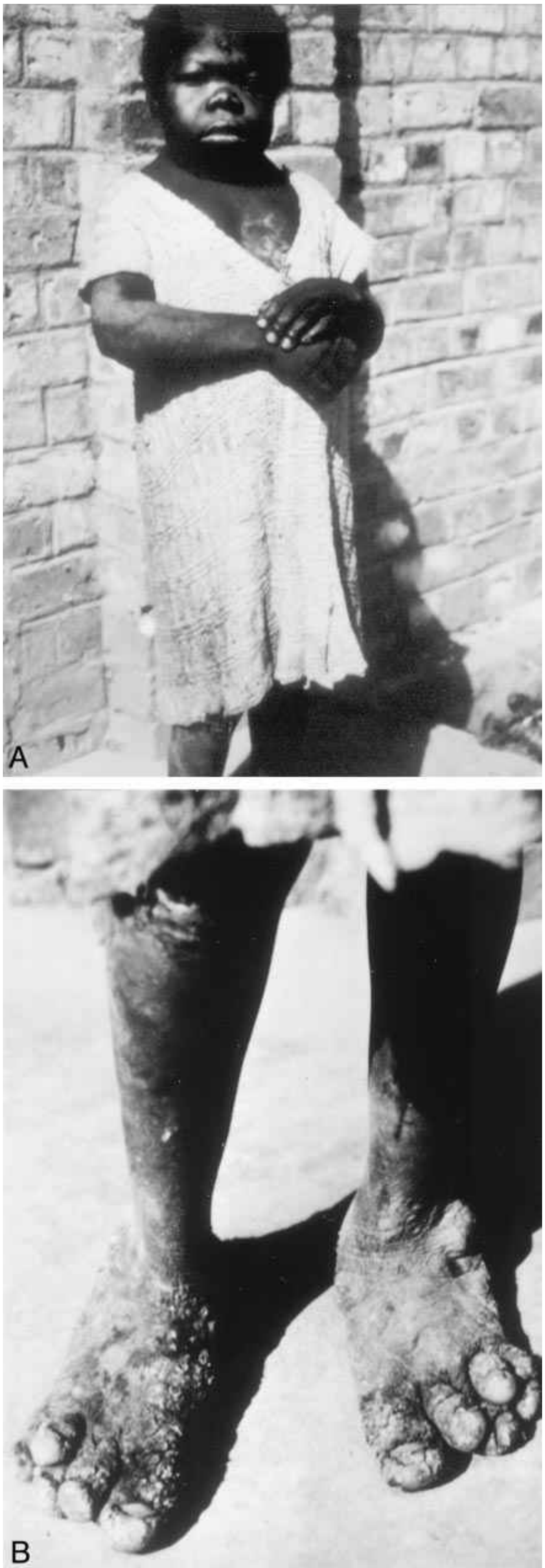

FIG. 7. Cretins exhibit a characteristic gait and station (A) with broad-based stance, exaggerated lumbar lordosis (B), splayed feet, and stunted broad digits.

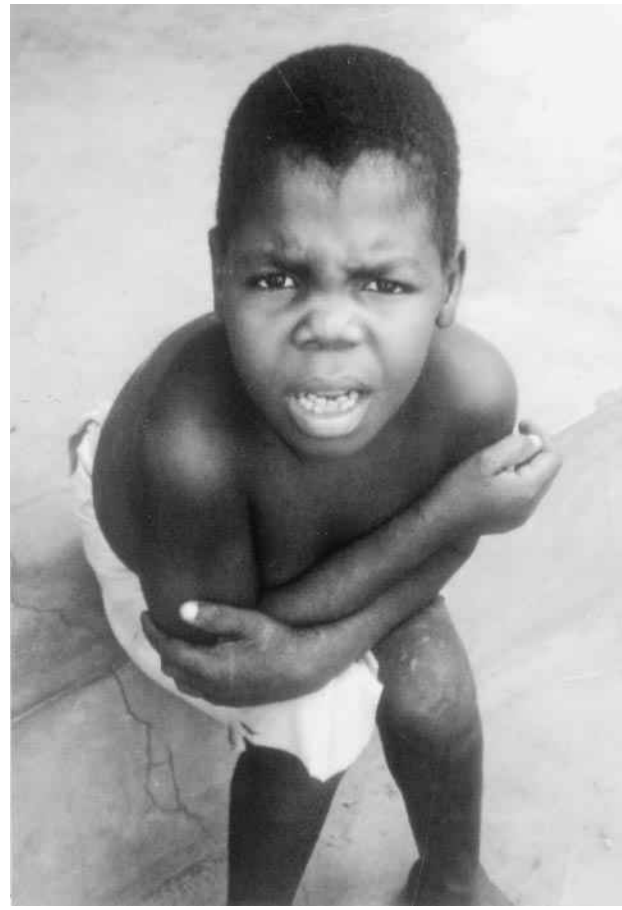

FIG. 8. Additional manifestations of cretinism can be seen in delayed development milestones, for example, exhibited here in retention of primary teeth as secondary teeth have erupted. (Note incidentally the white nail beds evidencing anemia.)

noassay, serum protein, selenium, iodine, and thiocyanate by chemical assay and spectrometry. Similar elemental studies were run on urine, thyroid tissue, and hair samples for iron, selenium, and iodine. In some subsamples, and for other purposes, human immunodeficiency virus (HIV) antibody determinations were done by radioimmunoassay. HIV seropositivity turned out on later examination to be undetectable in samples at the earliest samplings, but in the time period covered by the study, the virus entered the population through other geopolitical circumstances of the movement of outsiders through this previously isolated area in organized ivory poaching and counter-raiding[33] with the last determined incidence approaching 2.9% seropositivity.

Each of these goiter estimates was carried out on unselected members of whole village populations covering a wide spectrum of ages. All of the village of Ebale, and most of Assa and Ndamana, were surveyed. Each individual was followed over time with serial measurements made quarterly on a baseline of the population survey, and continuing in the intervention trial. Individuals were assigned a number on entry into the survey, and that was given to them on a small wooden block worn like an amulet (Fig. 13).

The assessment scale for populations described as marginally, significantly, or profoundly affected is shown in Table VI. By these assays of blood and urine constituents, the majority of

FIG. 9. Sexual maturity is delayed in cretinism, with the onset of ovulation often later than 30 y.

children in the population surveyed were profoundly iodine deficient.[3]

RESULTS OF POPULATION SURVEY

Goiter prevalence was nearly universal. The WHO Class III goiters predominated (Table V). In one village, not one adult who was not a cretin could be found without a goiter. Most of the population experienced the goiter itself as a benign condition, and accepted it as normal. Even some carved wooden figures or dolls were represented with goiters (Fig. 14). A random photograph of any group of people would reveal obvious WHO Class III goiters apparent at a distance in nearly all (Fig. 15). The estimation by one chief headman in a village called Ebale is that the population surveyed is 95% inclusive of his village population. This high prevalence of goiter appeared evenly spread through each decade of life.

An even more tragic preliminary finding from the population survey was an incidence of cretinism as high as 11% of the population. This number reflects the prevalence, that is, the number of surviving cretins, and discounts those so severely retarded that they did not survive birth or infancy. A potential bias was uncovered in the anomalously lower incidence in the village of Ebale when one of the elders from the village noted our special interest in two of the severely retarded neurologic cretins examined during the surveillance visit. This community leader said that he had been unaware of our interest in seeing all of the cretins, as well as those with goiters. Some cretins had been hidden outside of the village since they were not the "citoyens" of which the village was necessarily most proud. But when reassured that all of the population was to be included in village surveys, they understood that meant 100% of the accessible population. Once we expressed an interest in the entire population, a number of other cretins were presented, bringing the total up to the 10% that had been observed in other villages.

Some of the cretins were capable of limited self-care, but others were a burden on the society since they were unable to gather food or firewood or to draw water. However, to the extent that they were able, they were well incorporated into the society, and if trainable for minimal duties, were considered part of the community by necessity.

Measurements of thyroid function as determined by thyroxin and TSH in serum at population baseline revealed significant hypothyroidism in all the population and profound hypothyroidism in many. Even after averaging in one hyperthyroid individual encountered in a population of 50 (Table VII), the mean for the thyroxin determination (normal 4.5–12.5 μg/dL) was 3.12. Many individuals were encountered with thyroxin values of less than 1.0. TSH levels averaged 48.36 (normal 0.3–5 uIU/mL). A group of 50 individuals in one group of compounds that consisted of a small nameless village near Ebale was sampled in its entirety, and

FIG. 10. Clinical estimation of the size of the goiter in grams (A) was sharpened in precision by comparison with those specimens excised and weighed, and photographic confirmation (B) against a metric grid assisted serial follow-up determinations.

FIG. 11. Tissue paper is applied to the extended neck and an outline of the goiter is traced (A). This tracing is then digitized with a calibrated wheel in perimetry (B) and stored in the patient's record for serial observations in the longitudinal study.

the data from these individuals are presented in Table VII. Many individuals in this group of 50 illustrated in Table VII had TSH levels well over 100. In other individuals within our population survey, previously unheard of levels of TSH 1000 were encountered in profoundly hypothyroid individuals. Thyroid hormone levels found in a random selection of 11 cretins in this village demonstrate this profound hypothyroidism: TSH mean of 312.48 and T_4 mean of 0.88 (Table VIII).

INTERVENTION: IODINE REPLETION, GOITROGEN REDUCTION, AND THYROIDECTOMY IN SELECTED INSTANCES

Goitrogenesis is principally due to iodine deficiency in this area. Contributing factors, such as the presence of goitrogens in the food stock, that interfere with organification of iodine might make possible intervention through dietary advice. A global admonition to reduce their intake of cassava, the principal source of calories, would be fatuous and cruel, since this population is in marginal caloric balance to begin with. The poor equatorial soils of the rain forest support few grassland crops, and one of the principal advantages of cassava is the low human energy requirements for its gathering and semicultivation.

Even if alternate food stocks were available or introduced, and if they could be sustained in the marginal soils of the equatorial rain forest, their presence would lead to the classic "chicken and egg" dilemma. To invest the higher human energy needed for a much later yield of higher calorie basic food staples would not be easy given the current marginal subsistence levels, even if such substitution were ecologically possible.

When I have gone hunting with members of this population, volunteers to carry meat back from a kill are numerous. The parts most eagerly sought after are fat, often viscera, with offal preferred over lean skeletal meat. This reflects a craving for higher energy food value in animal fats. This craving for animal fats is rarely satisfied, given the marginal grazing capacity, the high incidence of Trypanosomiasis, and the heavy natural predation on and by large mammals in this wilderness area. Leopards and lions make livestock husbandry impossible, besides luring the predators close in to human habitation with the easy prey as bait. Elephant and buffalo herds can destroy a whole village's collection of shambas in a single night, ruining a year's effort at clearing and gardening. Hunting and gathering remain the principal sources of occasional high energy foods, and for a more predictable source of calories, palm oil is collected. Fats from animal or vegetable sources have similar energy content, but more craving develops for animal fat because of its flavoring and as an intermittent, unreliable supply of a special treat.

Most high energy foods are seasonal, and do not store well for the 5 mo of dry season, so the bulk of the population continues to subsist on cassava. Despite its low energy input, it has a low

TABLE V.

THYROID HORMONE LEVELS IMPROVED WITHIN MONTHS FOLLOWING DEPOT IODINE INJECTION AND PERSISTED FOR 3 Y IMPROVEMENT. THE PERIMETRY MEASUREMENT OF GOITER SHRANK FOLLOWING INJECTION OF IODINE, BUT REGREW AT 3-Y FOLLOW-UP, ALTHOUGH NOT TO THE SIZE OF PRETREATMENT VALUES

	Prelipiodol	6 mo Postlipiodol	36 mo Postlipiodol
Goiter planimetry	36 ± 16 cm	19 ± 13 cm	30 ± 12 cm
	(n = 149)	(n = 86)	(n = 59)
	P = 0.001	P = 0.001	P = 0.001
T_4 Hormonogenesis (norm 4.5–12.5 μg/dl)	3.49 ± 2.82 μg/dl		6.59 ± 2.53 μg/dl
	(n = 96)		(n = 54)
	P = 0.001		P = 0.001

Not all 149 patients had been followed 3 y at data analysis, and 23 were lost to follow-up.

FIG. 12. The use of height as an estimate for age is not reliable among cretins, as can be seen in an example of three individuals (A), ages 29, 10, and 16 y. Comparison of adult height reached (B) might suggest the dwarfism seen in neighboring Pygmy peoples.

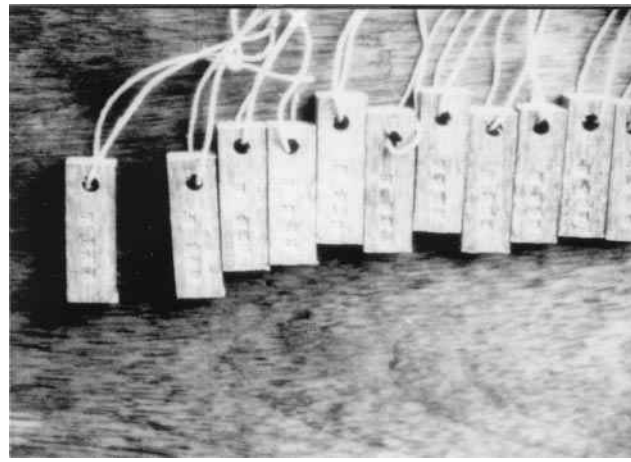

FIG. 13. On entry into the population survey, each participant was issued a wooden identification tag worn like an amulet.

energy capacity to which an adult in this environment is marginally adapted, given the hypothyroidism. Children, even *with* hypothyroidism, are macronutrient deprived, as well as micronutrient deficient in iodine, and have little energy reserves for enduring any intercurrent illness from the infectious agents that abound in this environment.

A high percentage of the world's food stock, in the field or in storage, is consumed by rats. In this region, baboons and buffalo, as well as rats, deplete the supply of rice and peanuts, but leave the cassava root in the field and in storage.

As dietary substitution is not always effective, perhaps advice on preparation of the dietary food staple would be appropriate. Rather than soaking the cassava roots in stagnant pits as seen in Figure 3, encouraging preparation by soaking the roots in running streams would seem to dilute and diminish the cyanide content in the course of the cassava preparation. This advice is counterintuitive to the majority of the population who would be principally concerned with losing some part of their food store in running water. This counsel was called "zungu za wazungu," kiSwahili for the "white man's madness," as were a number of other non-acculturated suggestions. Even if this advice were accepted by an educable population who could understand the reason for its recommendation, it could not be generally followed. The tropics are marked by two distinct seasons—the rainy season and the dry season—and advice on soaking in running water would be impossible half the year.

TABLE VI.

ASSESSMENT OF SEVERITY OF IODINE DEFICIENCY DISORDERS IN CHILDREN

	Marginal	Significant	Profound
Urinary iodine/creatinine excretion	50	25–50	>25
Goiter	20%	20–30%	$>30\%$
Serum T_4	3–8	3	very low
Serum TSH	4–6	6–10	10

T_4, thyroid status; TSH, thyroid stimulating hormone.

FIG. 14. Some indications of goiter as an accepted norm can be seen in carved figures or dolls that exhibit goiter.

If macronutrient supply is marginal and alternate preparation methods are impractical, what other methods might be employed to relieve the iodine micronutrient deficiency? In the developed world, the public health problem of iodine deficiency has been addressed by the simple, but largely effective, global response of replacing the deficient micronutrient in a ubiquitous, cheap, required nutrient. With the same rationale as adding fluoride to water or vitamin D precursors to milk for consumption by the population at risk, iodized salt was instituted over a century ago. This simple additive solution largely brought the problem of cretinism and goiter under control in the Western world, usually beginning with the high-frequency areas affected, such as the Great Lakes region of the USA and the volcanic mountain regions of Europe.

Iodine supplementation through iodized salt might be delivered by commercial food production methods and transportation systems in the market mechanisms of a cash economy. But the same geographic features of mountainous and/or rain forest terrain that isolate remote areas of the globe also expose food stocks to decomposition in periodic wet and dry cycles. These would reduce iodine content even if distribution systems were available. Salt itself becomes a precious commodity under these circumstances and, if available, would unlikely be given to vulnerable segments of the population, particularly children, who may not have yet acquired or developed a taste for this scarce and climate-sensitive condiment. Here, men eat first and children last, so foods cooked with salt would likely be consumed long before the children were served. In a barter society, commodities introduced from the outside become precious, and are often hoarded for exchange by the relatively wealthy. Salt and soap are *the* exchange commodities in Sasaland, which increased the value and decreased the consumption of salt, skewing its distribution to the wrong end of the risk population distribution. Thus, even when and if it were possible to iodize, protect, and deliver salt to the region, consumption patterns would mitigate against achievement of the desired outcome.

The most successful method of controlling of goiter and cretinism in this population turns out to be depot iodine repletion. Elemental iodine dissolved in poppyseed oil at a concentration of 480.0 mg/mL is already constituted in a product called lipiodol, originally produced for lymphangiography (Fig. 16). A depot injection of this iodized oil intramuscularly can completely replete iodine stores to eliminate iodine deficiency for a period of up to 5 y (Fig. 17).[34] Compliance is not a problem, nor does one have to worry that such iodization will not be shared with infants or childbearing women, since it is administered by the thyroid investigation team. Since the team was in control of the injection process, the needles and syringes were sterilized and the risk of HIV transmission was controlled by non-reusable needles that were destroyed. There were no alternative sources of readily

FIG. 15. A random photograph of any group of people shows WHO III goiters—the population norm encountered in this survey of remote villages.

TABLE VII.

POPULATION SURVEY DATA OF 50 PERSONS BEFORE AND AFTER INTERVENTION AND FOLLOW-UP*

	T_4 normal 4.5–12.5 μg/dL			TSH normal 0.3–5.0 uIU/mL		
Person	Preinjection	1 Inject	2 Inject	Preinjection	1 Inject	2 Inject
1	3.6	8.0	6.6	25.5	3.2	2.2
2	15.8	6.8	6.3	1.2	1.1	0.5
3	4.3	10.5	5.1	2.1	0.6	2.3
4	6.9	8.3	7.6	2.8	0.4	0.8
5	1.7	5.3	6.3	4.0	3.4	0.2
6	5.0	5.5	8.8	4.3	2.3	0.8
7	1.4	3.2	6.9	8.3	3.6	1.5
8	1.9	6.9	8.0	2.4	4.4	1.6
9	0.7	13.3	3.7	217.1	3.7	51.5
10	0.6	11.5	3.8	320.1	0.6	7.1
11	0.2	7.7	7.9	331.1	2.2	0.9
12	0.2	7.7	8.2	45.5	1.1	0.4
13	0.1	9.4	9.6	746.1	1.6	1.0
14	0.1	8.7	9.8	132.6	0.4	0.8
15	3.8	8.4	8.2	4.7	3.0	0.9
16	1.2	6.0	7.44	20.8	3.4	4.9
17	2.6	5.3	8.9	7.7	14.9	3.5
18	1.7	4.0	10.2	7.4	5.9	0.8
19	6.2	7.3	7.1	2.7	1.0	0.7
20	0.7	2.8	9.1	159.1	54.2	1.4
21	0.4	4.3	8.0	120.6	1.7	3.2
22	3.3	3.6	6.7	10.1	4.5	3.9
23	3.7	11.4	7.9	3.8	2.0	3.9
24	1.6	6.6	2.7	7.5	1.1	3.6
25	0.6	6.0	2.7	26.2	2.6	0.5
26	5.2	4.2	4.6	3.4	2.0	7.9
27	2.8	9.3	3.3	8.0	1.4	3.5
28	3.3	5.4	2.1	2.2	1.0	1.7
29	2.7	5.6	2.0	8.9	5.1	5.1
30	2.0	2.9	8.5	3.8	2.8	0.2
31	3.1	6.1	2.9	4.0	3.5	0.8
32	1.3	8.7	5.2	15.2	5.6	1.0
33	1.4	4.1	1.3	34.4	3.7	16.1
34	1.6	9.7	8.0	3.5	1.3	3.4
35	4.5	6.8	4.2	1.4	1.3	9.5
36	3.2	5.9	6.3	4.5	1.8	1.8
37	2.8	6.3	4.0	3.8	1.3	1.9
38	3.8	1.9	4.3	1.5	1.1	8.8
39	4.4	4.9	4.9	3.0	3.8	7.4
40	1.0	4.6	4.6	32.3	1.1	5.6
41	4.5	6.0	5.5	4.1	5.5	2.5
42	0.4	7.0	4.7	55.1	17.9	2.8
43	3.0	6.0	5.3	0.8	1.7	5.2
44	4.9	2.8	5.3	2.1	1.1	3.0
45	5.6	7.3	8.0	1.8	1.1	0.6
46	8.7	8.1	9.5	1.9	2.6	0.6
47	2.9	8.0	6.2	3.1	1.3	4.6
48	3.3	10.2	6.3	2.2	2.5	15.0
49	5.5	4.5	5.2	2.2	0.3	3.2
50	6.0	5.7	7.4	1.4	1.4	0.8
Mean	3.12	6.61	6.14	48.36	3.91	4.21
1 SD	2.68	2.45	2.25	123.81	7.83	7.57

* Comparison reveals a baseline T_4 averaging 3.12 (with many less than 1.0) and TSH averaging 48.36 (with many above 100.0) before any iodine repletion efforts.

T_4, thyroid status; TSH, thyroid stimulating hormone.

TABLE VIII.

THYROID HORMONE LEVELS OF MYXEDEMATOUS CRETINS FROM THE VILLAGE OF EBALE (RANDOM SELECTION)

Name	T_4	TSH
1. Panzio	1.0	171.7
2. Ruta	0.2	248.4
3. Jamboli	0.9	216.8
4. Malingo	0.8	392.9
5. Isolongu	0.4	395.0
6. Fongosende	1.2	586.6
7. Kufuo	1.5	40.6
8. Gasikpio	1.6	133.5
9. Antibotibe	0.8	628.8
10. Ngbogbo	0.8	337.0
11. Nafuo	0.5	287.7

T_4: normal 4.5–12.5 ug/dL; Mean 0.88; SD = 0.4. TSH: Normal 0.3–5 uIU/mL; Mean 312.48; SD = 181.3.
T_4, thyroid status; TSH, thyroid stimulating hormone.

FIG. 17. One intramuscular dose of iodized oil repletes iodine requirements for up to 5 y, and there is no question of compliance with treatment or maldistribution within the population, neglecting women or children at highest risk.

available iodine within this population. In addition, there was essentially no traffic or commerce from outside the group, since there was no transport or marketing of any goods to outside groups in a largely cashless economy. There were no other iodine sources available for barter within the Bas-Uele region.

RESULTS OF DEPOT IODINE REPLETION INTERVENTION

The population survey was completed for baseline determinations. Longitudinal study was carried out through serial observations at quarterly intervals, except when moved up to 1 mo to avoid the most difficult travel periods within the rainy season. Iodine repletion study was then begun for the treatment arm of the population under surveillance. The independent variable was the injection of 480.0 mg of elemental iodine in 1.0 mL of poppyseed oil in adults, children were treated with 0.5 mL, or 240.0 mg of iodine. Randomization was done by assignment from a book of random numbers to the serial distribution of "latte," or wooden tag amulets (Fig. 13). The treated group was compared with an untreated control population. The measurements of goiter, thyroid function, and other morphologic measures are reported herewith.

FIG. 16. Depot iodine repletion is possible by an intramuscular injection of 1.0 ml of 480.0 mg elemental iodine per mL of poppyseed oil.

Measurements of thyroxin and TSH in one sample population of 50 patients are seen in Table I. In contrast with the baseline in the untreated population at time zero, similar measurements done at 6 mo and at 3 y following lipiodol injection showed a doubling of the mean thyroxin levels into normal range, and a six-fold reduction in mean TSH determinations. Thus, hypothyroidism was resolved within a very short time following iodine repletion, and remained in normal range for 3 y.

In correlation with this change in thyroid hormone measurement that normalized from hypothyroid ranges documented before treatment, changes were observed in goiter that were equally impressive (Table V). As noted when compared from baseline control, goiter perimetry measures shrank remarkably when compared at 6 mo following lipiodol injection, yet increased significantly once again by the 3 y determination. At 3 y, the goiters were still remarkably smaller than they were before treatment, but they did not normalize as remarkably as the persistent improvement in thyroid hormone determination.

Additionally, there was a morphologic finding of an "escape" from the early beneficial effects of iodine repletion on goiter size that was a surprise discovery. As noted in Figure 18, nearly all goiters uniformly shrank in their planimetry measures, but in serial observations some appeared to escape this early control and regrowth was experienced. An analysis of 45 such patients who exhibited this regrowth is seen in Table IX. In this subgroup of 45 patients who exhibited this goiter regrowth, it was noted that the planimetry was reduced to half of the pretreatment measurements within 6 mo of injection. Of those studied at 3 y follow-up, the goiter had returned to preoperative size, a significant change in each direction.

That hormone levels remained in the normal range during regrowth of goiter shows the better compensation of thyroid hypertrophy when iodine has been repleted. In the absence of adequate iodine, pituitary TSH stimulation of goiter formation could mitigate severe hypothyroidism, but could never completely compensate bringing thyroid hormone levels to normal without sufficient iodine substrate. Following lipiodol ingestion, this deficiency was relatively corrected and the compensation is reflected in thyroid hormone levels holding near normal, even while goi-

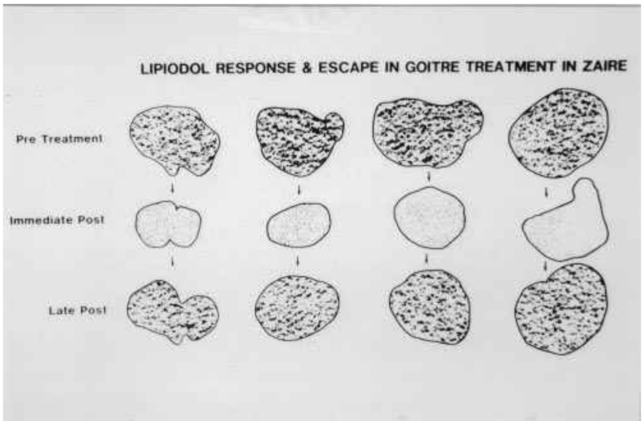

FIG. 18. In some patients, even those who remained normal in their thyroid hormone measurements, goiter regrowth was observed in escape from the effective shrinkage that followed iodine repletion.

terogenesis reflects the extra effort expended in maintaining them near normal.

Despite these morphologic markers of improvement in most of the patients, the subgroup that experienced goiter regrowth posed a new medical problem. A goiter, even a massively enlarged goiter that hangs down between the breasts in front of the manubrium, may be inconvenient and cosmetically disfiguring, but these complaints were minimized in this population. There was little functional derangement caused by an exophytic goiter. However, if such an enlarged gland shrank, retreated into the thoracic inlet, and then regrew, compromise to the airway and food passages became a real and increasing problem. As a consequence, patients were selected from the subgroup of those exhibiting intrathoracic regrowth and offered thyroidectomy for reduction of the morphologic as well as functional consequences of goiter regrowth.

THYROIDECTOMY FOR SELECTED PATIENTS WITH GOITER REGROWTH AFTER IODINE REPLETION

Carrying out a major operation in the conditions of a remote bush makeshift operating room might appear to be a formidable undertaking because of this low-technology environment. Previous reports suggested that it was possible for successful surgical therapy to be undertaken in remote settings[35] including the environment created at Assa.[36] Furthermore, the morphologic manifestation of goiter may be even more immediately life-threatening than the functional consequences in hypothyroidism if respiratory obstruction ensues.[37]

TABLE IX.

GOITER REGROWTH

Prelipiodol	6 mo Postlipiodol	36 mo Postlipiodol
36 ± 15 cm (n = 45) P = 0.001	18 ± 10 cm (n = 25) P = 0.001	36 ± 12 cm (n = 17) P = 0.001

Goiter planimetry was reduced in half for 43 patients who subsequently regrew back to original size at 3 y follow-up. Not all 45 patients had reached 3 y follow-up at the time data were analyzed, and 10 were lost to follow-up.

TABLE X.

PATIENTS UNDERGOING THYROIDECTOMY

Indications for operation:	
Impending airway obstruction	10
Massive Lipiodol-resistant glands	21
Chronic draining sinuses	2
Patient dissatisfaction with appearance	5
Thyroid gland removal median 0.5–1.0 kg (largest 1.8 kg)	
Thyroid gland remnant 20.0–30.0 g	
Deaths:	
Surgical 3	
1 postoperative airway obstruction (cretin)	
1 postoperative pulmonary embolus	
1 collapse second postoperative day, cause uncertain	
Medical 2	
1 suffocation	
1 thyroid storm	

Thirty-eight adults, representing 50% compliance of the 76 recommended for medical preoperative preparation with at least 4 d Lugol's solution (10 drops in water three times a day). Local anesthesia and cervical block (all), with Ethrane supplementation (four).

With the special challenges of tropical surgical conditions, subtotal thyroidectomy was undertaken in a select group of patients (Table X). As it may be helpful and instructive to show how an effective low-technology operating room environment may be improvised under such circumstances, Figure 19 illustrates the fundamental features improvised in such a tropical surgical setting. Instruments and surgical sheeting were prepared in a pressure autoclave heated over a wood fire for which both firewood and water were gathered from the forest by family members (Fig. 19A). The operating room light consists of a solar panel on the thatched roof that trickle charges a storage battery wired to a used automobile headlamp (Fig. 19B). Using local and regional anesthesia is possible in this very patient and long-suffering population. Cervical block was used in the majority of patients and intubation with draw-over ether in ambient air was used in others. Inhalation anesthesia was used in some with difficult airway compromise (Fig. 19C). Rigorously adhering to surgical principles while improvising appliances as needed,[38] subtotal thyroidectomy was safely undertaken in a group of 38 patients.

Pretreatment with oral Lugol's iodine solution was used to help decrease the hypervascularity of these iodoprival glands. Patients who are profoundly iodine deficient have a very high probability of serious hemorrhage from the hypervascular glands and should not be operated without the iodine pretreatment. Patients who are cretins are fragile in the perioperative period, and it is recommended that they be brought to euthyroid function by thyroid hormone replacement. Following iodine and hormone supplementation, the preoperative patients that have been prepared for surgery (Fig. 20A) undergo subtotal thyroidectomy leaving 20.0–30.0 g thyroid remnants (approximating the size of a normal thyroid) attached to an intact blood supply with care that parathyroid circulation is undisturbed and the recurrent laryngeal nerves are identified and protected. Using this technique, the thyroid function was preserved with removal of up to a kilogram of redundant gland (Fig. 20B) with close follow-up observation during recovery for a period of 48 h for airway protection (Fig. 20C).

The results of thyroidectomy appeared satisfactory for most patients with surgical mortality reflecting the fragility of some of these patients. While one of the patients with a compressive goiter

FIG. 19. Surgical principles are rigorously applied, but adapted to improvised appliances for safe surgery in remote tropical circumstances: a pressure cooker autoclave (A) prepares sterilized instruments and surgical light (B) is trickle charged from a solar panel to a storage battery wired to a used automobile headlamp. Local anesthesia was supplemented by draw-over ether general anesthesia (C) for those patients who required intubation.

FIG. 20. Pretreatment with Lugol's iodine solution for 5–10 d decreases size and vascularity of the goiters in the preoperative preparation (A) making subtotal thyroidectomy safer, removing up to 1.0 kg of redundant gland (B) with a brief period of recovery observation (C) to protect the airway.

was awaiting treatment in the absence of the surgical team, death occurred from airway collapse. A second death occurred from hyperthyroidism, made possible by iodine repletion in "Jod-Basedow's syndrome." Jod-Basedow's syndrome is hyperthyroidism acquired in a previously hypothyroid patient when iodine is "fuel added to the fire." In the hypothyroid patient with iodine deprivation, some autonomy may take over in thyroid hormone synthesis by this enlarged thyroid that allows escape from pituitary control. But, no synthesis of thyroid hormone can be achieved until iodine repletion. In a rare few patients, such repletion permits a flare of overproduction of thyroid hormone, overriding the pituitary shutdown of TSH usually seen in hyperthyroidism.

ASSESSING THE OUTCOME OF INTERVENTION IN MORPHOLOGIC CHANGES

Changes in form were dramatic in many of the measurements made. Thyroid hormone levels uniformly increased, and remained elevated with TSH suppressed through the longitudinal follow-up. Goiters shrank remarkably following depot iodine, but regrew on later continuing measurement. Some of these patients selected

TABLE XI.

NEUROMUSCULAR ASSESSMENT AS MEASURED BY HAND DYNAMOMETER GRIP STRENGTH TESTING

Population	Treated population	Untreated
Number	50	17
Mean	24.88 kg	22.0 kg
Standard deviation	18.5	14.6
Variant	4–42	2–48

Treated population is measured 3 y postlipiodol injection. The size of the dynamometer was adjusted to fit the individual's hand, and recorded to the nearest 0.5 kg.

TABLE XII.

NEUROMUSCULAR IMPROVEMENT AS MEASURED BY FOREARM REFLEX ACTIVITY

Pretreatment reflex	Posttreatment reflex	Number
Normal	Normal	51
Low	Normal	26
Low	Low	0
Normal	Low	2
High	Normal	9
Normal	High	2
High/normal	Low	10

Randomized population of 100. Assessment made at 3 y postlipiodol treatment.

underwent operation for reduction in risk of this structural compromise to their airway.

The changes in function were even more remarkable than those changes noted in form. The most dramatic change observed in the morphology of patients with already established goiter or cretinism was one very encouraging fact very early on in the study: in comparison with the control group, there was not one cretin born in the group of women treated by iodine repletion! The control arm of this investigation was immediately stopped for all women of reproducing age and was broadened for inclusion of most children approaching school age.[39]

Forty village leaders conducted a survey at 10 y from the first intervention (June 1993) and unanimously reported remarkably positive changes in each of the individuals who had iodine repletion. With respect to each individual treated, there was qualitative improvement (with the already noted exceptions of the complications of hyperthyroidism that were made possible by iodine repletion—a condition known as "Jod-Basedow's Syndrome"—and complications due to regrowth of intrathoracic goiter or other postoperative events). Statements made by those administering the program within Sasaland were very enthusiastic. Kongonyesi, the untiring logistical assistant for the extended project, said, "Thank you for the goiter project, it heals people very much, their minds and bodies as well." Of the other health initiatives attempted within this decade and this region, it is the most successful program in terms of compliance, sustainability, and behavior changes.

The immediate effect of medical intervention in relief of hypothyroidism is dramatic in individual terms. With the rare exception of some medical complications of over-activity (as in the rare events of Jod-Basedow's Syndrome) the effects of iodine repletion in nearly all individuals seem positive. Converting from the low-energy hypothyroid state to normal metabolic rate is a revolution in development potential measured in the individual patient. The individual successes within the program can be viewed in summation in smaller groups of that population before looking at the overall impact.

Neuromotor response change was measured by several functions. Table XI demonstrates the results of testing the grip strength with the right hand (the Azande of the Congo are permitted to be only right-handed) dynamometer for a population sample (n = 50). Three years following iodine repletion, the mean was 24.88 kg (SD = 18.5). A random sampling of the untreated population (n = 17) shows the mean to be 22.0 kg (SD = 14.6); the dynamometer was calibrated for each person tested.

Neuromotor function improvement was measurable in the forearm reflex activities: hypothyroidism is a status of depressed reflexes and subnormal response to neuromotor stimulus. The investigator's own reflex is assumed to be normal and the subject's rate of response is compared to it. Two plus is normal, one plus is delayed, and zero is profoundly retarded or absent. Three plus is brisk in rate of response and four plus is hyperactive. In a population sample of 100, 51% began at a normal response level and maintained that for 3 y following iodine repletion (Table XII). The 26% that began at a low response level increased to a normal level; there were none that remained at a low level of response. A subset of 10% responded initially at a high level, but at the 3-y marker dropped to a low level, substantiating other findings that the severe hypothyroidism treated by the 438.0 mg of lipiodol does not maintain euthyroid parameters for 3 y (Table XIII).

Fourteen individuals of the original population treated (n = 413) were hoarse before the iodine repletion; of these, 13 (92.8%) improved to a normal voice level within 6 mo postinjection. The one woman remained hoarse until she was treated surgically—a subtotal thyroidectomy relieved her of an 830.0-g goiter.

Three of the mute (but not deaf) cretins began talking within 6–12 wk postinjection. As all three lived in distant villages (more than 35 km) they were not influenced by the research team nor did they receive increased village attention, thereby escaping the

TABLE XIII.

CHANGES OBSERVED IN GOITER AND HYPOTHYROIDISM WITH IODINE REPLETION BY DEPOT INJECTION

Lipiodol	Prelipiodol	6 mo Postlipiodol	36 mo Postlipiodol
Goiter planimetry	36 ± 16 cm (n = 149) P = 0.001	19 ± 13 cm (n = 86) P = 0.001	30 ± 12 cm (n = 59) P = 0.001
T_4 hormonogenesis (norm 4.5–12.5 μg/dL)	3.49 ± 2.82 μg/dL (n = 96) P = 0.001		6.59 ± 2.53 μg/dL (n = 54) P = 0.001

Not all 149 patients had follow-up for 3 y at data analysis, and 23 were lost to follow-up.
T_4, thyroid status.

Hawthorne effect.* Several began drawing and many of them used tools for the first time.

THE "DOWNSIDE" OF THE IODINE REPLETION PROGRAM IN INDIVIDUALS AND THE SOCIETY—POSSIBLE NEGATIVE CONSEQUENCES OF CHANGES

There are few notable negative effects of iodine repletion when judged by morphologic criteria in the individual as well as the individual functioning results.

Measurements in form and function have shown dramatic change when viewed in the individual or in subgroups. These functional changes are not limited to the experience of individual patients, however, but in iteration become more than the sum of individual improvements within the community composed of these individuals previously suffering hypothyroidism. Some of these functional consequences may be surprising when considered collectively, even if predictable when viewed individually, since correction of hypothyroidism allows increased energy output and development, but also demands increased caloric input and creates remarkably increased fertility and enhanced resource consumption.

The measurements of hypothyroidism, goiter, and fertility in the neighboring Efe and Lese population showed that they were similarly affected with hypothyroidism (Table II).[25] Fertility was low in both the study population at the outset of the survey and in the Pygmy population as exhibited in the Table III (unpublished observations). Fertility is multifactorial, with component parts being the rate of secondary infertility based in pelvic infectious disease, caloric sufficiency with adequate nutrients to accumulate a fat surplus in women sufficient to commence and sustain ovulation, and other factors such as duration of breastfeeding.[40] There is no evidence that the rate of pelvic inflammatory disease or breastfeeding practices changed during the study interval in the population under surveillance, but fertility certainly increased.

Not only did fertility increase, but maternal and infant mortality decreased, resulting in an overall increase in the population. Each of these population members were also increased consumers, since caloric intake adequate for the minimal energy output of a cretin is not adequate to sustain a person with normal thyroid status and normal metabolic demands. The caloric requirement increased by at least a third for each of the individuals treated when they were relieved of hypothyroidism, and the increased number of these enhanced consumers has meant greater demand on the environment within the study area. Food production from that which is grown or gathered was marginal at the time of the original survey and not remarkably increased despite efforts to do so following medical intervention and the notable population increase during the period of the study.

The effects of medical intervention on the society as a whole have tempered the conclusions of an overall success in terms of individual improvement following medical intervention. As dramatic as the measurements of morphologic markers in individuals, the functional consequences were no less impressive both for individuals and the society composed of those affected when hypothyroidism was corrected. Energy output increased, learning ability improved, coordination and skills increased, and efficiency and ambition were demonstrated in initiation of some development projects planned and initiated following this medical intervention.

However, energy requirements also increased. Subsistence based on a once daily cassava staple was no longer adequate, and enriching dietary elements were sought with special hunger for animal fats. Ground nuts came to be in higher demand, but required more energy input in cultivation and soil improvement. More of the forest surrounding the small village was slashed and burned for increased garden plots, and people walked further for food, firewood, and water. Even in this region of sparsely settled scarce resources, there were scattered groups encroached upon by the expanding demands of the coalescing compounds in Sasaland.

And Sasaland is no longer small! Compounds have become villages and villages have become crowded. A letter sent by a chief informant announces in amazement: "It seems every woman is pregnant." Fertility has soared, even among cretins whose anovulatory cycles had previously limited their fertility, and whose stunted stature had made delivery impossible, requiring C-section. Not only has fertility increased dramatically, but elimination of neonatal cretinism has caused the stillbirth rate to plummet. Both maternal and infant survival rates have changed dramatically from the time previous to the medical intervention when cretins were laboring to deliver cretins, often with the loss of both.

The population has doubled within the 8 y of the initiation of treatment, and the new members of this population pyramid, heavy at the base, are both quantitatively and qualitatively much better consumers.

The most readily observable change has been in the environment. What had been a series of forest clearings with scattered hut compounds have become a large confluent regional village and there is considerable degradation of what had been a typically luxuriant tropical forest ecology. Four streams, no longer adequate, are now also polluted. Latrines had been built, but are now crowded past capacity, and children, particularly, do not use them. Agricultural intensification is unlikely because of scarce poor soils on mostly volcanic rock, now denuded of much of its forest cover through slashing both for firewood and more garden space.

The dire economic circumstances of civil warfare in Zaire's general economy and its hyperinflation had little effect on the people previously, since they were outside the cash economy, foraging for almost all their needs. Now, some families are sending forth migrants to try to find whatever urban job environment for which their unskilled distant rural experience may have qualified them. The nearest city is far away with uncertain transport; the beginning point of any mechanized transit mode is several hundred kilometers away. Such transport would require cash in an unstable currency rather than the barter that has been their usual economy. If they return, they may bring back deadly social diseases, as one has already.[33]

DISCUSSION

Human Ecology Dependent on Environmental Factors

Biologic adaptation to environmental factors is not a new concept in human ecology.[41–43] Trace elements, especially iodine, are well studied in their distribution in the terrestrial environment[44] and in their variation in human nutrition.[45] Soil resources may directly effect human habitation in the tropics in their organic component[46] and micronutrients.[47]

Iron and cobalt are necessary parts of human dietary intake to supply substrate for hemoglobin synthesis, and anemia can crudely influence human capacity for aerobic calorie utilization also, but less directly than the rate-limiting supply of iodine on metabolism that is finely attuned through thyroid hormone synthesis and secretion. Iodine is a necessary component of the metabolic regulator itself and iodine deficiency has an amplified effect greater than that seen with macronutrient calorie deficiency or micronutrient deficiency such as iron, which only indirectly contributes to a normal metabolic rate.

*The Hawthorne effect is noted when members of the studied population alter their behavior to produce the outcome thought to be desired by the researchers.

Disease Disadvantages

It is very easy to understand how certain conditions called "diseases" adversely affect human energy utilization, often by interfering in normal regulatory processes that control energy expenditure. A classic example is fever, which entails excessively high energy consumption not typically purposefully directed and quite often injurious when uncontrolled, such as in febrile seizures in children.

This is true for many, if not most, infections and parasitic infestations; it is highly likely for degenerative diseases that are inflammatory, proliferative (such as buildup of atherosclerosis), neoplastic (almost all cancers can lead to the end of the individual's life), and degenerative diseases that lead to loss of organization and coordination (such as neurologic disorders and strokes).

Disease Conferring Advantages

Despite the counterintuitive nature of the concept, certain diseases are seen to confer advantages on the human host, usually in reference to some particular environmental stress. If the advantage is not evident to an affected individual, it might be seen as beneficial in conveying a survival advantage to future offspring. Perhaps the most clearly elucidated of these groups of "adaptive diseases" are some forms of blood dyscrasias. These include enzyme deficiencies such as G6PD (glucose 6-phosphate dehydrogenase) and cholinesterase deficiencies.

Best described are the hemoglobinopathies[48] such as sickle cell anemia, thalassemia, Mediterranean fever, and polymorphous forms of each. These abnormalities in hemoglobin synthesis can lead to deformation of red blood cells, anemia, and circulation disorders that may be lethal diseases in and of themselves, but particularly under the additional stress of hypoxia, such as that which occurs at higher altitudes or during arrested or slowed circulation. Using the example of true sickle cell anemia, there is no adaptive advantage of the homozygous patterns of the disease no matter where its victim lives. Sickle cell anemia is a classic unmitigated disease, with enough associated morbidity that it should have been naturally selected out of the population as distinctively disadvantageous.

Genetic Predetermined Disease

But two factors coincide to conserve sickle cell anemia. First is the fact that it is not a classic Mendellian dominant characteristic and requires sickle hemoglobin inheritance from both parents for the true sickle cell disease; the heterogyzote is not severely affected by disease, and is instead characterized as having "sickle cell trait." This detectable abnormality confers a survival advantage on the person who bears it, given the second factor in the environment—malaria. The often lethal falciparum malaria parasite cannot readily infest the red cells composed of sickle trait hybrid hemoglobin, so this heterozygous condition confers a relative resistance upon the carrier to malaria infestation. Sickle cell trait, therefore, is favored in tropical regions of high falciparum endemnicity, whereas people with the sickle cell anemia are susceptible to lethal anemia crises and people with normal hemoglobin are susceptible to a lethal form of malaria. The sickle hemoglobin is a disease conserved, therefore, because it confers adaptive advantage to coexistent falciparum malaria—and the incidence of the two diseases can be drawn on coterminus maps.[48]

Acquired Disease

Two important distinctions are drawn in comparison with the conserved diseases of sickle cell hemoglobin and hypothyroidism that make them remarkably different. The hemoglobinopathies are familial, and are inherited as genetic characteristics. In fact, the genetic mutation in the case of sickle hemoglobin has been defined down to a point mutation in a single base pair that gives rise to the synthesis of the abnormal sickle hemoglobin. Penetrance and expression of the sickle gene is high and sickle cell anemia breeds true, with little evidence of amelioration of the disease state by other biologic adaptations. Hemoglobin status is genetically determined, does not remarkably interfere with fertility, and is congenital—a term that will be used to mean literally that one is "born with" the condition. Genetic differences that can be passed on and environmental adaptive advantage are the two kinds of ingredients evolutionary biology can work with over time to select in, or out, those genetic predeterminants that are more, or less, adaptive.

Hypothyroidism on the other hand is acquired. Within an adult individual's lifetime, or, indeed, within a short period of treatment, it can be abolished—and was, within a generation of iodized salt introduction in the West, and within the period of observation in this study. Earlier, and largely discredited, suggestions[49] held that there may have been "a genetical [sic] factor in endemic goiter," but this has been disproven by several lines of evidence. First, hypothyroidism is a state of reduced fertility: the more profound the hypothyroidism, the less able the individual is to reproduce. Second, the disease is curable in the adult, and no transmission of the disorder then occurs in the offspring.

But, is not cretinism congenital? Yes, in the sense that the term's literal meaning is to be "born with" the disorder; but it is not genetic and familial. Cretinism is a disease acquired in utero, and such profound failure to develop may occur that cretinism may be irreversible at the time it is recognized and treated after birth. Even cretin women, if they are iodine repleted and should happen to become pregnant can be delivered of a neurologically, metabolically normal offspring, even if the treatment came too late in the mother's life to reverse the mental retardation experienced in her own period of in utero development.

An example that can be used to illustrate a non-genetic acquired abnormality in the adult that might also be present congenitally in a child is hypertrophy of the heart muscle, the myocardium. In sports medicine, athletes are seen who after a period of conditioning and training have developed myocardial hypertrophy in order to compensate for the increased demand of the work load of distance aerobic effort, such as marathon running. The same abnormality may be found in the newborn with a ventricular septal defect at birth, whose myocardium hypertrophies to accommodate the increased flow of shunted blood. In both instances of hypertrophy of the myocardium, and in the similar phenomenon of thyroid hypertrophy, some genetic traits may have rendered the individual more susceptible to the stress, but the abnormality is fundamentally an acquired one, and it can be eliminated from the somatotype by treatment without the genotype conveying this trait in the absence of similar stress.

Without a genetically determined trait that would be transmissable through unimpaired fertility, evolutionary biology lacks the two levers of natural selective advantage under circumstances of environmental stress.

Nutrient Environmental Stress

One of the environmental stresses that has been common in nearly all parts of the world at one time or another has been caloric insufficiency. Famines have occurred from pole to equator under environmental circumstances from drought to glaciation. There is little suppportable claim that starvation induces hypothyroidism, but rather that those who have hypothyroidism are better adapted to reduced calorie intake. Iodine-deficient environments have the highest incidence of hypothyroidism—acquired, not inherited, in such a micronutrient milieu—and in such environments hypothyroid individuals could better withstand what would be for individuals with normal metabolism, macronutrient insufficiency.

As with the endocrine manifestations of diabetes that even in the adult-acquired form has a genetic predisposition, there may be a genetic predilection for goiter or for cretinism in some instances. The fetus seems to preferentially sequester more than the maternal share of iodine—and this is evidenced by the large goiter growth during pregnancy of some women under observation in this study who delivered babies who were marginally compensated, or at least not florid cretins. Cretinism was prevented by a shifting of the scarce iodine to the fetus at a cost of a more severe adult-acquired goiter; this compensation may be genetically predetermined.

This would reflect an acquired biologic adaptation to energy-resource-poor environments on the part of those individuals whose energy requirements were minimized by their depressed metabolic rates acquired by micronutrient iodine deficiency. Decreased fertility is a collective biologically acquired response that further decreases demand on caloric resources.

Coincidence, merely by chance association, is an improbable explanation for the fact that hypothyroidism is found in highest incidence in the world's calorie resource-poor regions. Coincidence is also an unsatisfactory explanation for why regions of endemic hypothyroidism have not developed as intensely into complex societies, taking into consideration the effect of this decrease in human energy utilization.

Biologic Adaptation

Biology is not the only human factor modifying these environments or the activities within them. Environmental biology alone[50] is not the single, or even most important, adaptive response. Beyond this acquired biologic adaptation are the inheritable variation advantages of natural selection processes of classic Darwinism,[51] and beyond that are the social[52] and cultural aspects.[53] Each of these other adaptive processes might require separate legitimate study and each may be more powerful than the acquired biologic adaptation. Cultural response can be employed to overcome biologic disadvantages.

Medical Intervention as Maladaptive

One such cultural response is medical intervention. But if medical intervention disturbs the metabolic adaptation through micronutrient repletion without also addressing the consequence of macronutrient sustainable repletion, it is inappropriate. A vertical program focused on micronutrient iodine repletion alone, whether in the confines of this population under study or in a global campaign solely for eradication of iodine deficiency represents medical intervention that is metabolically maladaptive.

THE LIMITS OF MEDICAL INTERVENTION IN IMPROVED DEVELOPMENT

The Congo (ex-Zaïrian) population under longitudinal study in Sasaland is adjacent to the Ituri population of Efe and Lese who have been resident in the region for much longer than the Azande. The Efe and Lese live in an environment of similar iodine deficiency. Yet as noted in our observations (Table II), the goiter prevalence among the Lese was 34.1% and Efe 5.7% compared with 83% in Bas-Uele (Table III) and nearly 100% in Sasaland. Goiters found among the Efe and Lese were of smaller size by WHO classification than the nearly uniformly large WHO III goiters in Sasaland.

Only one previous report has noted the anomalously low endemic goiter prevalence among Efe Pygmies.[24] Explanations of the difference in prevalence rates among the nomadic and village-settled Pygmy populations are presumably due to some adaptive mechanism within the Efe. As noted in Table II, a pituitary factor is demonstrated since both TSH and insulin-like growth factor (IGF) are significantly correlated with ethnic origin, both peptides relating to metabolic rate, and each respectively correlated with goiter and growth in stature.

In the pretreatment population surveys among Azande (Table VII), hypothyroidism is noted by a mean T_4 of 3.12 μg/dL that more than doubles after iodine repletion to 6.61 μg/dL. The very elevated TSH in response to this hypothyroidism is more than ten-fold increased over normal (mean 48.36 uIU/mL) before treatment, but drops by over 100% to a normal mean of 3.91 uIU/mL after iodine repletion among the treated Azande. By contrast, the Efe were less hypothyroid (12.1 μg/dL thyroxin) than Lese (11.4 μg/dL thyroxin); both groups had much better thyroid hormone values than the Azande. They also exhibited normal TSH values. Furthermore, they had a much lower goiter rate (Table I) with less than 5% for Efe and 35% for Lese compared with 100% for a comparable sample population of Azande.

The measurement that might partly explain the low incidence of goiter in Efe is the higher urinary iodine, nearly twice the level of that seen in Lese. But, a very interesting datum pointed out herein (Table II) is the highly significantly lower levels IGF-1 levels among the Efe, less than half the values for either Lese or Azande. This growth factor IGF-1 as well as TSH are low in Efe, and each has implications speculated upon as the reason for diminished stature among Efe.[1] It may also mean that IGF-1 is a required cofactor for goitrogenesis, which Efe have less of than Lese, and both express less than Azande.[54–56] Azande, except for those who are cretins, have a height and stature comparable to other Bantu populations in Central Africa.

The Efe may have evolved a cultural means of mitigating hypothyroidism through an interdependence that furnishes a greater variety of micronutrients and macronutrient food resources.[57] Reliance on a monoculture, particularly one that is low in calories, profoundly deficient in iodine, iron, selenium, Vitamin A, and protein, and contains a goitrogen that may be further concentrated in its preparation, renders the Azande peoples within this study population vulnerable to hypothyroidism.

The Efe interdependency with Lese may give them a greater variety of food resources than the Azande experience. The lower rates of hypothyroidism and goiter observed within the Lese than the Azande demonstrate may reflect the greater variety of food resources, including enough iodine to bring their thyroid hormone levels up to nearby levels (Table II) but through the hypothyroidism-induced compensatory mechanism of goiter incidence in one third of the Lese. The Lese may either be more dependent on cassava food stock and its goitrogen potential than Efe, or the Efe, if they have a comparable cassava intake as Lese do, are selectively spared by the combination of low TSH and IGF-1 factors for goitrogenesis.

Although each of the three populations lives in an iodine-deprived environment, only the Azande are nearly exclusively dependent on cassava with its goitrogen and the Azande demonstrate both extremely high TSH and normal IGF-1 with resultant nearly uniform goitrogenesis. The Efe may lack one of the factors necessary for predictable goiter formation in the low IGF-1 levels they exhibit, even if they were exposed to goitrogens and depended on a less-varied source of caloric intake.

CONCLUSION

Changing one aspect within this ecologic adaptation, namely micronutrient iodine repletion, without modifying means to improve nutrition in macronutrient and other micronutrient sources constitutes a further maladaptive stress upsetting the marginal benefit of low energy utilization and requirements.

When evaluating the effect on an individual of iodine repletion in the correction of hypothyroidism, medical intervention seems to have a very obvious and overwhelmingly positive beneficial consequence with exceptions that are considered complications. When viewed from the perspective of the society of which these individuals are a part, the negative consequences of medical intervention in hypothyroidism become more prominent.

Spokespersons for the Azande population under study, including those not involved as participants, such as Chief Sasa, are uniformly appreciative of the medical intervention program in hypothyroidism when viewing the results in individual lives. But they have expressed increasing complaints about the circumstances of their poverty, environmental degradation, crowded conditions, hunger and restlessness. Such conditions are not interpreted as related in any way to the hypothyroidism intervention, though they are coincident in onset.

In much the same way as evaluation of morphologic consequences of intervention in an iodine deficient population can have beneficial, detrimental, and surprising consequences, (e.g., goiter regrowth through some other mechanism in escape from iodine repletion), the functional consequences in the society have been even more so, since this micronutrient deficiency is embedded in a society adapted to marginal macronutrient supply. Isolated correction of one deficiency disorder may uncover others (as already suggested with vitamin A), and create a transient maladaption if carried out in the absence of an overall development program.

A surgical intervention program for goiter reduction would not be meaningful except in the context of a medical program for the control of other disorders, and both of them combined would be more meaningful in the context of a public health program in which iodine deficiency control is one element of a more extensive program. The control of this micronutrient deficiency itself is meaningful when viewed in the context of overall development in human potential and resource utilization in the environment in which these deficiencies are encountered. Beyond measurement comes understanding of the context in which iodine deficiency disorders have been conserved, and careful intervention should include close support and observation of predictable as well as unanticipated consequences that may be encountered.

The observations of this longitudinal study in hypothyroidism, and intervention in at least one of the factors giving rise to it, lead to a conclusion that hypothyroidism itself has adaptive advantages for resource-poor environments in which micronutrient and macronutrients are deficient. It is in just such environments that hypothyroidism has its greatest prevalence, where low human energy utilization is compatible with survival.

The reversal of this hypothyroidism, correctable by medical intervention, has changed both individuals and the society in this remote resource-scarce environment. It is an instructive lesson in both the potential and limitations of medical intervention in a complex human social problem.

It may be that hypothyroidism, though considered a disease—and surely disadvantageous to development in individual and collective social terms—is adaptive to resource-poor marginal environments. In this equatorial environment, the need for clothing, shelter, energy fuels, and high-energy food stuffs is all quite limited, and hypothyroidism fits in these unique circumstances. Because it is adaptive to such a marginal environment, it has been conserved and, not by coincidence, it appears in the world's poorest populations in the most marginal of habitats. Hypothyroidism not only limits energy requirements, but also fertility and population pressures that might otherwise outstrip available resources.

The Azande peoples who were the principal subjects of this study are relatively recent arrivals in this region compared with the longer term residents, Efe and Lese. They are also more severely affected by the consequences of iodine deficiency, with exposure to this deficit comparable among each of these groups in the same environment. This may reflect the better adaptation of the longer term residents in accommodating this nutritional stress, suggesting such improved adaptation might also become possible for the Azande, even if no major change in iodine availability were to occur.

The biologic balance between energy resources available and those consumed in human activity may tilt on the fulcrum of iodine. In an environment in which caloric potential is marginal, the concomittant deficiency of this trace element, iodine, may fix a lower set-point in the steady state for conservation of energy balance. This biologic balance should be appreciated before a cultural intervention is initiated that might upset the adaptive features that allow this balance to be drawn. Medical care in such circumstances may be maladaptive and should be undertaken cautiously as a component of a culture-sensitive development program to mitigate the change in this adaptive metabolic pattern.

ACKNOWLEDGMENT

The author would like to thank Diane C. Downing, RN, MPH, for her help.

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