

## Endemic cretinism—a continuous personal educational experience during 10 years

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THE processes involved in the progress of scientific knowledge have fascinated philosophers, scientific workers and non-scientists. Kuhn (1970), in his interesting essay on the structure of scientific revolutions, sees the road which the growth of scientific knowledge follows, not marked by discoveries but by what he names paradigms, 'theories that gain their status because they are more successful than their competitors in solving a few problems . . .' which are recognized as acute. Examples of paradigms in biology are, e.g. Berthold's conceptualization of endocrinology in 1849; Mendel's theory of inheritance; Medawar's concept of immunological tolerance, etc.

At the start a paradigm promises success with the application of the concept to the field concerned. The activities, then, of 'normal science consist of the actualization of that promise, an actualization achieved by extending the knowledge of those facts that the paradigm displays as particularly revealing . . .'. This frequently requires the development of new techniques. 'Few people who are not actually practitioners of a mature science realize how much mop-up work of this sort a paradigm leaves to be done, or quite how fascinating such work can prove in the execution. . . . Mopping-up operations are what engage most scientists throughout their career'.

Today I intend to tell you something about such a mopping-up operation. The process of scientific activity itself is a subject of discussion, with extremes of romantic and rational views. I am not trained in philosophy, and do not intend to present pros and cons of different theories. This is a theme on which much provoking material has been written, e.g. by Medawar (1967). My personal experience fits best with his description of the hypothetico-deductive process, which consists of a moving to and fro between hypothesis and experiments or observations.

It is the purpose of my presentation today to

dissect roughly my learning experience in the subject of endemic cretinism of the past 10 years in such a way that the considerations which shaped our activities are laid bare and may be of use to others engaged in clinical research. This unusual way of reporting activities may detract merits from other investigators. In the past 10 years several groups (Australians, North and South Americans and Belgians) have worked on these problems. They met together at least five times, and jointly published three monographs with reports of their discussions—'Endemic goitre' Stanbury (1969), 'Endemic cretinism' Hetzel and Pharoah (1971), 'Human development and the thyroid gland' Stanbury and Kroc (1972). As in any field of investigation, the thinking progressed collectively. The Belgian group contributed much insight in the function of the iodine-deficient gland, and the clinical picture of the myxoedematous form of endemic cretinism. The successive Australian investigators discovered the value of iodized oil injections as an alternative and successful method for prophylaxis. They also introduced the idea of three motor milestones (sitting, standing and walking unaided) for the recognition of cretinism at an early age. The South American workers studied mainly nervous cretinism, the duration of iodine prophylaxis with iodized oil, and the chemical data of mother-fetus relationship.

This story starts in 1962. At that time we had already worked on thyroid problems for about 20 years. A Dutch doctor (Van Rhijn) who had spent 4 years in Western New Guinea (now Irian Barat) showed us photographs of goitrous people in the Mulia valley in the Highlands of Western New Guinea, and told of their mental backwardness and hearing defects. He persuaded our group to visit that area. Choufoer and Van Rhijn participated in this expedition for about 5 months, and myself for a shorter period. The questions posed were obvious: is this iodine deficiency and endemic cretinism?

What did we see? Figures 1-3 give an impression of affected people. They belong to the Dani tribe, living in the neolithic age without wheel and pot, and they suffer in this area from severe goitre and mainly neurological abnormalities.

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FIG. 1. A young woman of the Dani tribe with severe endemic goitre.

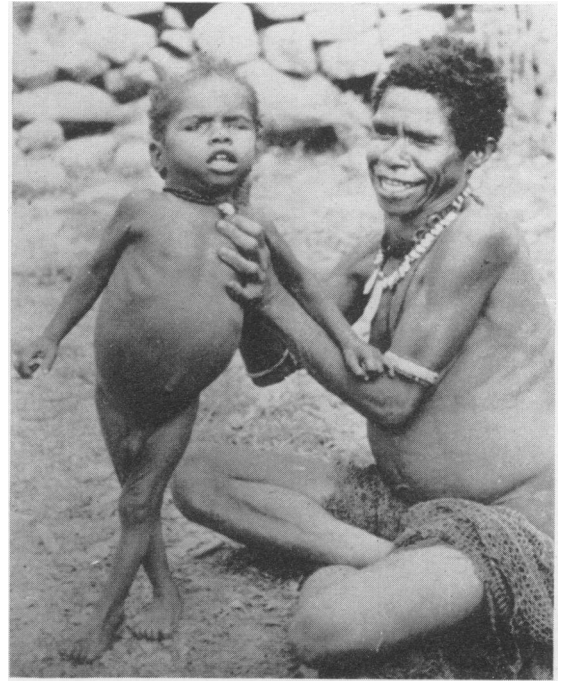


FIG. 2. Deafmute child, age 5-6 years (first permanent molar) with spastic diplegia, unable to sit or stand unaided. Severe mental deficiency and deafmutism. This was one of the rare children who were short (77 cm), and at later analyses appeared to have a skeletal age of about 1 year.

Our first and most difficult problem was that the syndrome of abnormalities we observed did not fit with what we thought should be endemic cretinism. We had of course read studies on endemic cretinism published around 1900. What we saw was indeed endemic cretinism, and it was identical with some previous descriptions. We expected to see what are generally called 'typical cretins', patients who are of short stature and mentally retarded. This is the picture of congenital hypothyroidism in Western countries. This picture was so engraved in our minds, that we were not sure at all that the abnormalities seen in Mulia could be classified as endemic cretinism. It later appeared that the same could be said for other investigators interested in thyroid disease. After we had completed our studies, we had great difficulty in convincing others of our conclusions, even after demonstrating the older descriptions of endemic cretinism! When reading the older literature we apparently were not prepared to recognize that the picture of endemic cretinism was different from sporadic cretinism!

This is of course the analogy of a well known psychological experiment, where in a deck of cards

TABLE 1. Prevalence of goitre and biochemical findings in Mulia, Central Highlands, New Guinea (Choufoer *et al.*, 1962)

	Mulia valley	Tiom valley
No. of inhabitants	1426	±5000 (sample 1000)
Goitre rate		
6-12 year (male and female)	20%	
Over 12 year: male	50%	Absent
female	80%	
Defectives	6%	Absent
Urinary 24 hr I µg	<5 <i>n</i> =47	13.6 ± 1.8 <i>n</i> =14
PBI µg%	1.7 ± 0.3 <i>n</i> =47	6.3 ± 0.2 <i>n</i> =15
Urinary nitrogen g/24 hr	2.5	
Perinatal death rate	15%	
First year death rate	30%	

some cards carry the spades coloured red, and some cards with hearts coloured black. This will not be recognized immediately and may even confuse. The major findings in the Mulia valley are summarized in Table 1. The goitre rate was high, 6% of the people were seriously defective (mental retardation, hearing loss, neurological abnormalities in varying

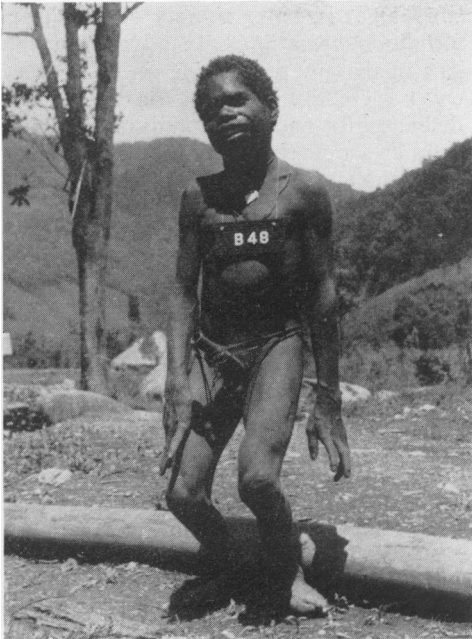


FIG. 3. Boy, 14 years old, imbecile, deafmute, severe squinting, flexed knees, normal skeletal age. The 24 hr  $I^{131}$  neck uptake was 90% and the serum PBI=1.7  $\mu\text{g}/100$  ml.

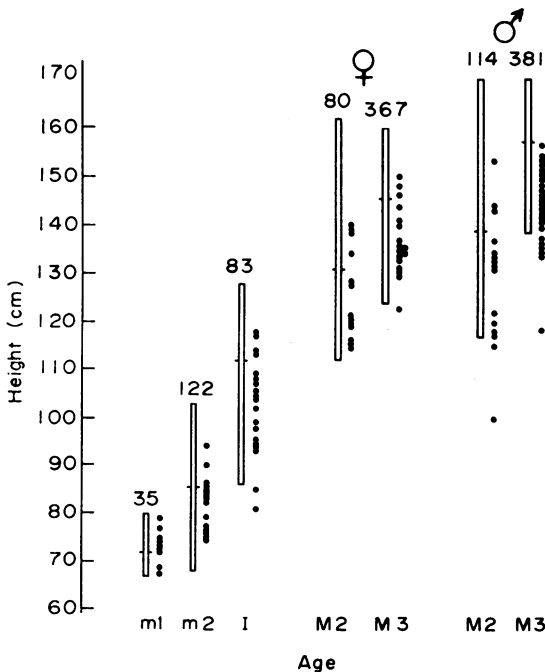


FIG. 4. Height vs dental age, for the Mulia area, of 'normals' (□) and defectives (●). As a group the adult defectives were shorter than the normals. Average height of thirty-four male adult (M3=adult dentition) was 145 cm. The average height of 381 adult normals was 156 cm.

degree and combinations). The 24-hr urinary iodine excretion was extremely low, and the average PBI was in the hypothyroid range. Figure 4 shows that, with a few exceptions, the defective people were not short! (Choufoer *et al.*, 1963; Choufoer, Van Rhijn and Querido, 1965; Van Rhijn, 1969).

Because we did not recognize the clinical picture, we had to remove the bias of calling it cretinism and we introduced a neutral term instead, calling the affected people *defectives*. This sounds simple but I can assure you that it was a difficult decision. It also immediately increased the number of possible causal factors, such as genetic, infectious and nutritional in a wider sense. If in a population one sees a great variety of symptomatology, the next step is to describe it in detail and to carry out, after some pilot observations, an epidemiological study examining *all* subjects in the population. And, furthermore, as one is not familiar with the ordinary pathology of such a rural population, it is necessary to compare the findings with a nearby control group, living under identical environmental conditions, but giving the impression of being unaffected. This control group was found in the nearby valley of Tiom, where goitre was practically absent, and no defectives were seen.

On what grounds did we decide that we had re-discovered the picture of endemic cretinism? We were lucky to find that about 50% of the people living in Mulia were born elsewhere, in a goitre-free region such as Tiom. We also found that a number of Mulia women had given birth to normal children in such a goitre-free region and, after moving to Mulia, frequently gave birth to endemic cretins. This observation is of course difficult to evaluate statistically; therefore, the finding that all endemic cretins of the Mulia valley were born in the severely goitrous region was more important. This information allowed several conclusions. The birth of endemic cretins was entirely geographically located and, furthermore, the importance of genetic and infectious causal factors became most unlikely because populations of different valleys mixed. The composition of the diet of the different valleys was also roughly identical, so that a positive noxious factor seemed unlikely. Putting all this evidence together, the conclusion that we were facing endemic cretinism was made on the following considerations: (a) genetic, infectious and noxious nutritional factors were unlikely because of strong mixing of people living in the Mulia Valley with those of goitre-free areas; (b) the birth of defectives was sharply determined geographically; (c) the presence of extreme iodine deficiency was established; (d) the clinical picture was identical with old descriptions.

In our work in the field we decided on three lines of approach. Firstly, to take as much bias away as we could through the use of the term 'defectives'.

Secondly, to approach the problem as an epidemiological study, and thirdly, to do it through the introduction of a control group.

After we had analysed the data at home, the publications had to be written. We were then faced with more difficulties. (1) What is the definition of endemic cretinism? (2) If mental retardation is essential for diagnosis, how did we know that the non-cretins had a normal learning ability? The same question presented itself for hearing loss. (3) Why did these people with low serum PBI not display clinical hypothyroidism? (4) In Mulia, no paralysed people were seen older than about 6 years. What was the reason for this age limit?

There were many other questions raised during our first discussion in 1965, with the Belgian investigators who had seen a different clinical picture (Bastenie *et al.*, 1962). The abnormalities observed by them conformed with the myxoedematous type of endemic cretinism described by McHarrison. We attempted to answer these defined problems.

#### The definition of endemic cretinism

This can be approached roughly in three different ways. The definition can be based on aetiology, on a basic morphological or physiological lesion common to all defects, or it can be purely of a descriptive nature. As the basic lesion in the cells of the affected organs in cretinism is unknown, only two possibilities are open. As to *aetiology* it is possible to say that endemic cretinism is geographically limited to areas of severe endemic goitre, but endemic goitre is not necessarily accompanied by endemic cretinism. The relation between the two diseases may therefore be a common cause, or the result of two factors, of which one leads to endemic goitre, while the other causing endemic cretinism is only effective in the presence of severe endemic goitre. Until now the only convincing evidence for the cause of endemic goitre points to iodine deficiency. This is also supported through the effectiveness of iodine prophylaxis. It does not exclude the possibility of more than one factor being present in endemic goitre. It is, for example, possible that with a borderline supply of iodine other factors are provocative. At this state of knowledge we came to an aetiological definition which, in fact, is of an *epidemiological* nature: 'Endemic cretinism is the collective term for a number of developmental abnormalities, which geographically coincide with severe endemic goitre and are caused by lesions acquired before or shortly after birth. More precisely, it may be defined as the excess of these abnormalities, which is found in a goitrous population, as compared with a similar population without goitre and, in due time, is abolished by adequate goitre prophylaxis' (Choufoer

*et al.*, 1965). It is, however, very difficult to make this definition operational. In all subsequent discussions of the groups working on endemic goitre and endemic cretinism, the aim was to use a *descriptive* definition for endemic cretinism. These discussions can be summarized with the statements of the Goroka conference in 1971 (Hetzel and Pharoah, 1971).

It was concluded that two major components in the syndrome of endemic cretinism are recognized: damage of the central nervous system, and the presence of hypothyroidism in different degree. 'The damage to the central nervous system shows clinically: (a) mental retardation; (b) perceptive deafness; (c) neuromotor retardation; (d) brain stem damage. The underlying pathology is largely unknown. On the basis of existing observations one may conjecture about likely areas of neuropathology. Additional clinical data such as more psychometry and more neurological investigations are required.'

With regard to the second component, hypothyroidism in different degree, this was further specified in the following way: (a) the most severe clinical form of hypothyroidism will be manifest as true myxoedema. Less severe forms may not present myxoedema, but stunted growth and delayed ossification; (b) chemically, hypothyroidism will be recognized by assays which show too low circulating thyroid hormone levels, or data indicating a failure of regulation of thyrotropic hormone.

This descriptive definition, although practically useful, can limit the recognition of abnormalities which are a consequence of iodine deficiency in the population as a whole. The possibility exists, for instance, that single abnormalities are present in the population which go unnoticed, such as moderate mental retardation or only moderate hearing loss. Should they not be called endemic cretinism?

#### The definition of mental retardation

Mental retardation is characterized by a decreased learning ability and insufficient social adaptation. Formerly, more general definitions were used, such as describing as mentally retarded those incapable of receiving proper benefit from instruction in the ordinary schools by reason of a defect of mind. However, in the British 'Wood report' in 1929 (cited by Penrose, 1963) a mentally defective individual was defined as 'one who by reason of incomplete mental development is incapable of independent social adaptation'. The second part of this definition obviously leaves much room for variation. In a rural community the scholastic defect is much less of a handicap than in a city or an industrial area.

For the measurement of learning ability, many

different tests have been developed, of which the Binet and Simon test, which is widely used, closely relates to scholastic success. The Binet test score is usually expressed in the form of the intelligence quotient, or I.Q., whereby the measured mental age is expressed as a percentage of the chronological age. Generally it is accepted that the distribution of the I.Q. in a population is Gaussian, with a mean of almost 100, and a standard deviation of 15 points. If one accepts this Gaussian distribution for intelligence, it can be decided that any score outside twice the standard deviation from the mean is exceptional. Theoretically this demarcation can be set at I.Q. of 70 which means that 2.3% of the population has a lower I.Q. than 70. In studies of populations it appeared that this theoretical estimation is slightly too low, because the curve is skewed to the left. In the Netherlands it is assumed that about 3% of the school-age children are unable to follow ordinary primary schools. The nomenclature used for individuals with I.Q. lower than 70 and down to 50 is feeble-minded; imbecile for scores between 20 and 50, and idiot when scoring below 20. Feeble-minded may develop a mental age of 7–10 years, while imbeciles are guessed to reach a mental age of 3–6 years.

The scores for intelligence tests are based on vocabulary and/or perceptual data. Both groups of tests, designed for Western cultures, cannot be used in different social or cultural surroundings. Intelligence tests are not cross-culturally applicable for many reasons, such as the different way reality is perceived, and because of environmental factors, such as poor nutrition, lack of intellectual stimulation, and other factors (Trowbridge, 1972). Culture free tests do not exist, but some are 'culture fair', which are tests avoiding the more obviously culture-bound features.

Both in sporadic and in endemic cretinism the mental retardation (with possible rare exceptions in endemic cretins) is the most significant abnormality. Endemic cretins as seen in rural areas in developing countries are, in fact, clinically diagnosed mainly because of lack of social adaptation. In such an environment this becomes only apparent when learning ability is very limited. This aspect may be the explanation why sometimes the frequency of endemic cretinism is reported to be only 1%! For it seems plausible that the biological variation of intellectual ability is the same as in Western countries, which means that 2–3% of the population is outside the mean  $-2$  s.d. Most of these feeble-minded, therefore, probably go unnoticed, and only the grossly retarded people and cretins are counted in these low percentages. These considerations make it quite possible that in such communities many more individuals (non-cretins) exist, who are mentally subnormal but socially well adapted.

The question of assessing hearing loss in the non-cretinous part of a severely iodine-deficient population is straightforward in sophisticated surroundings where it can be solved by audiometry. The constraints present in field work are obvious both with regard to skilled medical personnel and to the possibility of bringing and maintaining sophisticated equipment.

#### **Why did these Mulia people with low serum PBI not display clinical hypothyroidism?**

The diagnosis of clinical hypothyroidism in our environment is made on the basis of careful taking of histories (sensitivity to cold, fatigue, change of voice, coarseness and dryness of hair, sluggishness, change of menstrual period, constipation), physical examination and on laboratory data. Information from history in these rural areas is practically absent. Pronounced myxoedema will be noticed but mostly one has to rely on the laboratory information. The recent introduction of the serum triiodothyronine and serum TSH assay has shown that the area of subclinical to clinical hypothyroidism is very wide. It is even debated whether an increased serum TSH stands for hypothyroidism or whether it may also occur in a state of compensated clinical hypothyroidism. We conjectured, of course, that increased serum  $T_3$  levels (which then could not be determined) were a likely explanation for the absence of clinical hypothyroidism. These remarks on information based on history and on laboratory data show that clinical hypothyroidism may have escaped our attention in Mulia.

#### **Why are paralysed subjects in Mulia not seen older than 6 years of age?**

This brings in another determinant or complication of what may be encountered in such areas. In later studies in Ecuador we found a few adult deaf-mutes with paraplegia in a village with severe endemic cretinism. Evidently they were very carefully cared for by their families. In the Mulia Valley, children are nourished by their mothers for 3 to 4 years until the time that they are more or less able to take care of their own feeding. We therefore assume that these severely affected individuals simply died after the age of about 6 years because of absence of care.

These four questions with regard to the definition of endemic cretinism, the diagnosis of mental retardation and hypothyroidism, and the paraplegia, came more into focus in the course of recent years. During that period we also started to hypothesize about the pathophysiology and mechanism through which endemic cretinism was caused. We followed the hypothesis that the only known physiological action mechanism of iodine was through thyroid hormones. At least three sensitive periods for thyroid hormone deficiency can be recognized in human life. We know

from congenital hypothyroidism, leading to sporadic cretinism, that brain development during fetal life is sensitive to shortage of thyroid hormone. On the other hand it is accepted in clinical medicine that children who become hypothyroid after the third year of age, will be slow but their mental development is not impaired. Another known fact is that linear growth is impaired in thyroid deficiency. It is, however, unknown what degree of thyroid deficiency is required to cause these effects. Recently much more has become known through the work of Dobbing (1975) about central nervous system development in the early postnatal years. There is a pre-growth spurt period of cell division between 10 and 18 gestational weeks. However, the human brain growth spurt is predominantly postnatal. Human 'brain cells' as a total population continue rapid multiplication well into the second postnatal year, and rapid myelination continues even longer. From experimental evidence one may conclude that protein synthesis in the brain, myelination and neural interconnection depend on adequate thyroid supply. Again, how much thyroid supply is needed, we do not know. Recent experiments in chickens (Bargman and Gardner, 1967) and in mice (Deol, 1973) on inner ear development also have demonstrated the necessity of adequate thyroid supply for normal development.

The fact that in a severely iodine-deficient area not all children are endemic cretins but that a mother in the same environment also gives birth to normal children, indicates that the developmental processes described must be subject to fluctuations in thyroid supply in different degree and during different periods. This hypothesis offers an explanation for the variation in symptomatology of those subjects that are classified as endemic cretins, but also supports the supposition that in a severely iodine-deficient population subclinical forms of endemic cretinism may exist.

It was against this background of facts and hypotheses that we accepted the opportunity for co-operation with the medical faculty of Diponegoro University of Semarang, Indonesia, to investigate an area having goitre and endemic cretinism not far from Semarang, Central Java. This was an unusual opportunity because the logistic circumstances for investigation were much more favourable than during studies in previous regions of endemic goitre and endemic cretinism.

After 2 years of preparation by Dr R. Djokomoeljanto of Semarang in the village of Sengi, which consisted of acquiring the confidence of the people and mapping out the endemic goitre area in several aspects, we were able to move in with a combined team from Leiden Medical Faculty (Professor D.

Smeenk, Dr B. M. Goslings and myself), Dr G. Hennemann from Rotterdam Medical Faculty, and the members of the Medical Faculty of Diponegoro University.

First, the objectives for the study were defined and the plan of study was developed accordingly. In general terms the objectives were directed towards studying the pathology of the cretins and especially of the non-cretinous part of the population. The aim was to detect what kind of demarcation of symptomatology existed between those classified as clinical cretins and the non-cretinous part of the population and, more specifically, whether or not mental retardation, hearing loss and hypothyroidism were present in the non-cretinous part of the population.

Evidently, it was necessary to choose simple methods but also for the purpose of comparison to know what can be considered as normal for a rural area in Central Java. The criteria for obtaining information with regard to 'normality' had even to be restricted to a community with the same socio-economic development and environment. The methods chosen were measuring *hearing loss* with a Philips pure tone screening air conduction audiometer type PH 8726. Otoscopy was done in all subjects. For the assessment of clinical *hypothyroidism* the usual symptomatology was studied, with the addition of the measurement of 'half relaxation time' of the ankle jerk (reflex time) with a photomograph.

For measurement of *mental development* the Raven coloured progressive matrices test was chosen, which is considered to be a 'culture fair' test (Biesheuvel, 1969). We also wanted to investigate whether loss of thyroid function, which is the predominant pathology in Congo cretins, is an abnormality which is also present in the non-cretinous part of the population in an area severely deficient in iodine. If this were so, hypothyroidism would not be essential for the diagnosis of endemic cretinism. Besides these measurements, data on age, sex, height, weight, iodine excretion, neck uptake of radio-iodine, serum triiodothyronine, serum PBI and serum TSH, serum cholesterol and serum proteins were also collected. The question of what is normal for a community without iodine deficiency and with the same socio-economic development was answered by collecting data from such a population. A village named Londjong was thought to be a good control village, because of absence of goitre and endemic cretinism, and for the similarity of some social indicators as listed by Djokomoeljanto (1974) (Table 2).

The design was such that the data were collected in a random sample of about 50% of the population in both villages of the age group of 5-20 years (excluding the clinical cretins).

The 24-hr urinary iodine excretion in Sengi was

TABLE 2. Comparison of Londjong and Ngampel (Sengi)

Indicators	Londjong	Ngampel
Male/female	211/240	258/328
Rice fields (ha)	22.2	23.3
Non-rice fields (ha)	27.5	24.6
Village tax (Indon. Rp.)	49.743	41.494
Number of primary schools	None	None
Number of farmers (%)	99	100
Mountainous	Yes	Yes
Altitude (approx. metres)	600	500
Distance from main road (approx. km.)	1	1
Goitre rate	Less than 3%	85%
Endemic cretinism	Absent	7.5%

16±8 µg s.d./g creatinine and the PBI values of the non-cretinous population in Sengi were 2.5±1.4 µg% s.d. For the control village Londjong these values were respectively 42±18 µg/g creatinine and 5.0±1.1 µg%. The distribution of the age and sex subgroups studied in both villages was almost identical. From the average PBI values in the control village Londjong one may conclude that these were subnormal. However, no elevated serum TSH levels were found in the Londjong population. This showed that it was a good 'control' village, which at worst was in a state of fully compensated iodine deficiency.

The clinical diagnosis of endemic cretinism was arbitrarily made for subjects if at least two of the three following abnormalities were present: mental retardation; neuromotor abnormalities; bilateral hearing loss. Hypothyroidism was not used because we assume that this represents postnatal thyroid failure.

The results of the *hearing tests* were highly interesting. In the control village only one subject had a slight hearing loss for 4000 Hz at 20–30 dB. In Sengi, the situation was practically the same. Out of about twice the number of subjects examined, there were two subjects with this finding. If one subtracts the data of the control village from the findings in Sengi, the conclusion is that no hearing defects were present in the non-cretinous population. To be more accurate, in Sengi there were four individuals found with bilateral hearing loss who also had either neuromotor abnormalities or mental retardation. They were removed from the so-called normal group, and classified as cretins, because of the presence of two abnormalities (Goslings *et al.*, 1974).

*Reflex time* findings supported the conclusion that part of the non-cretinous population was hypothyroid. When interpreting the data, it should be taken into account that only 66% of the myxoedema patients show a reflex time more prolonged than the mean ±2 s.d. of the normals. Of the Sengi non-cretinous population, twenty-two subjects were outside the 2 s.d. of Londjong (= 317 msec), and seven of these were clinically hypothyroid (see Table 4; Djokomoeljanto, 1974). In the cretinous group (*n*=41) there were twelve clinically hypothyroid patients. *Mental performance* as measured with the Raven coloured progressive matrices test showed highly interesting indications in support of our suspicions. For each age group the means of Londjong and the Sengi NCP were compared by means of Student's test. If the result of these tests are combined, a very significant difference (*P*<0.01) in favour of the control village Londjong is found. These data strongly suggest that the non-cretinous part of the population in the severely iodine deficient area is slower in development.

Summarizing these findings it became clear that one abnormality, such as hearing loss, is not present in that part of the population in the affected village Sengi which is considered as being non-cretinous. On the contrary, the symptomatology of impairment of mental development and hypothyroidism form a continuum with the so-called normal population in Sengi. Pathophysiology offers the possibility for hypothesis. The abnormalities may be the result of intra-uterine damage, early postnatal hypothyroidism and adolescent hypothyroidism. The presence of hypothyroidism can easily be understood. If iodine is only available below a minimum for normal thyroid hormone supply, this may cause hypothyroidism. It also may lead to impairment of postnatal development of the central nervous system. Apparently adequate development of the hearing system is completed before birth, and the presence of hearing loss points to intra-uterine damage. Whether pathology other than hearing loss, in the clinical cretins, such as mental retardation and neuromotor abnormalities, are pre- or post-natal, is open to speculation.

This, then, is my story of the 'mopping-up' operation. The outcome has several aspects. From

TABLE 3. 'Reflex time' in msec in the Sengi non-cretinous population (NCP), in cretins and in the control village Londjong

	<i>n</i>	Mean	s.d.	Range	Prolonged reflex time	Hypothyroid clinically	%
Sengi-NCP	93	288.9	44.9	207–420	22	7	32
Sengi-Cretins	21	303.7	46.2	237–435	15	4	27
Londjong	33	261.7	27.5	215–310	—	—	—

Analysis of variance: *F* (2; 144)=6.83; 0.001 < *P* < 0.005; *SCr* > *SNCP* > *L*.

the public health point of view it has been shown that in a severely iodine-deficient area, a considerable percentage of the population not only has chemical hypothyroidism, but may also have abnormal physiological parameters, such as prolonged reflex time, indications of mental retardation and, if carefully examined, clinical signs of hypothyroidism. There are no such groups as *normal* and *cretin* in such an area.

A second outcome is a clarification of where we stand with the terminology and the descriptive definition on endemic cretinism. The first possibility is to apply the term endemic cretinism for all single or combined abnormalities, even when mental retardation is absent. In that case, the term cretinism is very wide and has no resemblance to sporadic cretinism. The second possibility is to reserve the term endemic cretin, in analogy with the use of the term sporadic cretin, for subjects with mental deficiency. It then follows that the abnormalities as seen in severely iodine-deficient areas have to be described to consist of cretinism (i.e. mental retardation) and other abnormalities, such as hearing loss, neuromotor abnormalities and hypothyroidism, each occurring alone or in combination. We prefer this second approach, although in fact the prevalence of cretinism in such areas becomes higher than formerly suspected.

You will have noticed that I did not discuss other details, such as serum triiodothyronine and serum TSH levels, radio-iodine uptake, and their correlation with other findings. I omitted this information not only because of time but also because I wanted to eliminate non-relevant data and to concentrate on the line of thinking and the design of the studies.

In the introduction I expressed the faint hope that my presentation might be of some use for others engaged in clinical research. Therefore I want to conclude with my own learning experience. Firstly, the work confirmed again what Sir Thomas Lewis said 40 years ago in a small book *Clinical Science* (Lewis, 1934), 'the attempt to reach accuracy of definition is itself a strong stimulus and powerful guide to investigational work'. Secondly, these studies showed the impact of constraints with regard to the limitations of possible techniques and size of team. This may of course be frustrating, but it also has a positive effect. The limit on team size brought a kind of despecialization for the team members. The constraint on techniques made it necessary to strike a balance between sharply defined objectives for the investigations, and the choice of simple techniques which were sufficient to penetrate into the problem. We all know that this should be done but the availability of many diagnostic possibilities in Western countries sometimes tends to loosen the grip on the objectives of the study. I also remember

two bits of advice given to me many years ago. One was from Dr J. Aub from Boston, who about 50 years ago was one of the first clinical investigators to conduct metabolic ward studies. He simply said 'if you want to study acromegaly, make sure that your patient who is being studied indeed has acromegaly'. I daresay we indeed studied iodine deficiency. The second remark comes from André Lwoff and runs as follows: 'For biological research the most important aspect is to define the problem, and the question that follows, clearly. If it is an important question, you may learn the necessary techniques, which may cost much time. In principle one can master any technique, but it is a loss of time to do so if the problem is not well defined'.

Finally, there is no new paradigm! But there is something else—a strong impetus to push iodine prophylaxis for countries which need it.

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