

THE EFFECT OF IODINE PROPHYLAXIS ON THE INCIDENCE OF ENDEMIC CREPINISM

P.O.D. Pharoah, I.H. Buttfield, and B.S. Hetzel

Institute of Human Biology, Goroka, Papua, New Guinea
Department of Nuclear Medicine, Queensland Radium
Institute, Brisbane, Australia. Monash Medical School,
Brahman, Victoria, Australia

It is generally accepted that dietary iodine deficiency is the major factor in the etiology of endemic goiter in most areas of the world. The effectiveness of iodine prophylaxis for endemic goiter was firmly established by Marine and Kimball (1) in a controlled trial in Ohio and has subsequently been confirmed by programs of salt iodization (2,3), iodization of bread and water supplies (4) and the intra-muscular administration of iodized oil. (5,6,7) Other factors are also known to influence the incidence of endemic goiter, e.g. dietary goitrogens (8), hardness of water supplies (9,10) and also perhaps water pollution (11). These factors are almost always superimposed on a dietary iodine deficiency.

The association between endemic cretinism and endemic goiter is a geographical one in that endemic cretinism is only found in areas where goiter is endemic. This fact is incorporated in the definition of endemic cretinism as given by the Pan American Health Organization (12). An endemic cretin was defined as an individual with irreversible changes in mental development, born in an endemic goiter area and exhibiting a combination of some of the following characteristics not explained by other causes:

1. Irreversible neuromuscular disorders
2. Irreversible abnormalities in hearing and speech leading in certain cases to deaf-mutism;

3. Impairment of somatic development
4. Hypothyroidism.

The correlation between dietary iodine deficiency and endemic goiter and the geographical association of endemic cretinism with endemic goiter has naturally led to the postulate that dietary iodine deficiency is of importance in the etiology of endemic cretinism. The main support for this postulate has been the remarkable disappearance of endemic cretinism when iodine prophylaxis is introduced to an area. This was well documented by Wespi (13), who correlated the incidence of deaf-mutism in the various cantons of Switzerland with the quantity of iodized salt consumed. More recently Buttfeld and Hetzel (14) following up the work of McCullagh (5), reported that eleven endemic cretins were found who had been born since iodine prophylaxis was introduced into the Huon Peninsula in New Guinea, but none were born to women who had received depot iodine injections.

Opponents of the iodine deficiency hypothesis have pointed to the fact that endemic cretinism was on the decline in certain countries prior to the introduction of any form of iodine prophylaxis. Costa *et al.* (15) report such a decline in the Piedmont in Italy. The census figures from the Argentine Republic reported by Greenwald (16) show a striking decrease between the years 1869 and 1914 in every province. Koenig and Veraguth (17) state that the disappearance of cretinism preceded by 10 years the introduction of iodine prophylaxis. Norris in 1847 (18) documented an endemic of cretinism in the village of Chisleborough, England, yet by 1871 he stated that cretinism in Chisleborough had almost died out (19). It appears that social and economic development in any country leads to the disappearance of endemic cretinism; Trotter (20) has criticised the study of Wespi on this ground. He points out that the negative correlation between the incidence of deaf-mutism and iodized salt consumption occurred at a time of active social change, so that other factors may have been responsible for the decline in deaf-mutism.

Until 1966 no controlled trial of iodine prophylaxis on the incidence of endemic cretinism had been carried out. Difficulties in controlling the use of measures such as iodized salt or iodide tablets were paramount. The introduction by McCullagh (5) of a single intramuscular injection of iodized oil and its proven effectiveness over a period of years (6) made a controlled trial more feasible. As a result, such a trial was instituted in the Jimi Valley of New Guinea where a high incidence of endemic cretinism had been reported. A preliminary report on the results has already appeared (21).

SUBJECTS AND METHODS

The Jimi is a remote valley in the western highlands of New Guinea which had its first contact with Europeans in 1953. Until 1970 this valley could only be reached by light aircraft or on foot. Some villages are now connected by vehicular roads, but access to the majority is still by walking tracks only.

The population of the valley is about 24,000. Individual villages have between 250 - 1,000 people, and lie at altitudes between 800 to 2,000 meters above sea level. The people live as homesteaders with houses and gardens scattered throughout the valley. Each village group has its own central meeting place.

Until very recently the economy of the people has been a subsistence one only.

In 1966 a controlled trial to determine the effectiveness of iodized oil as a prophylactic measure against endemic cretinism was commenced. From August to October, a patrol was carried out in conjunction with the local administration who were conducting a census. It covered 27 villages in the upper and middle valley with a population of 16,500. At each village all the people were assembled and a record made of their names and an estimate of each person's age. Women of child-bearing age were asked if they were pregnant. If so, this was recorded but no formal confirming examination was made.

Goiter size was assessed as reported previously (21). Grade 0 is no enlargement. Grade 1 is a palpable but not visible enlargement with the head in the normal position and Grade 2 is a visible enlargement of the thyroid with the head in a normal position. The prevalence of Grade 1 plus Grade 2 gives the goiter rate (GR) and the prevalence of Grade 2 alone gives the visible goiter rate (VGR).

Alternate families were injected with either iodized oil or normal saline, each member of the family receiving four ml if aged 12 years or over and two ml if under the age of 12 years. The nature of the injection given was recorded on the census sheet. Each milliliter of iodized oil contains approximately 400 mg of elemental iodine.

Follow-up patrols were carried out in July, 1967; November, 1969; January, March and November, 1970 and January, May, August, November, December, 1971. Due to the remoteness of the region only thirteen of the original twenty-seven villages,

with a population of 8,000, have been followed up. On each occasion all mothers and children in each village were assembled and checked against the census sheets. Infants born since 1966 were identified, their names and birth dates recorded. Birth dates were obtained from a variety of sources, from mission infant welfare records, from administration council records and from records kept by indigenous Aid-Post Orderlies stationed in some of the villages.

Each child was examined initially without knowledge of whether the mother had received oil or saline, primarily for evidence of motor retardation. The milestones assessed were those of sitting, standing and walking. Motor retardation was assumed to be present if these milestones were not attained by the ages of 12, 18 and 24 months respectively. In addition, the parents of all children were questioned as to whether they thought hearing and speech were normal. If they thought there was any abnormality of hearing or speech or if there was any motor retardation, a more formal attempt to assess deafness was made by having the child's attention distracted and noting if there was any response to a tuning fork, a snapping of fingers, or a hand clap. Auroscopic examination of the ear drum was also carried out to exclude otitis media.

A squint if present was noted. A more careful assessment of the extra-ocular movements was made in those children who were retarded in their motor milestones or had abnormalities of speech and hearing.

RESULTS

Table 1 gives the comparative goiter rates and visible goiter rates in the oil injected and the control groups. There were no significant differences in the numbers of males and females or in the goiter rates in these two groups.

Table 1. Goiter incidence in the population group studied for effect of iodized oil prophylaxis

Goiter Size	IODIZED OIL			SALINE		
	Total Population 3180	Males 1535	Females 1645	Total Population 3063	Males 1476	Females 1587
Grade 0	2540	1383	1157	2463	1355	1108
Grade 1	249	79	170	257	74	183
Grade 2	391	73	318	343	47	296
G.R.*	20.1%	9.9%	29.7%	19.6%	8.2%	30.2%
V.G.R.**	12.3%	4.8%	19.3%	11.2%	3.2%	18.7%

* Goiter rate

** Visible goiter rate

The number of children born to mothers who had oil or saline and the numbers of children who had died are given in Table 2. The latter figures are not accurate, particularly for the period July, 1967 to November, 1969 when the villages were not visited. Many of the children who were born and died during this time would not have been recorded.

Table 2. Birth data in relation to prophylaxis programs

Mother's Status	Total Births	Living Children	Deaths
Iodized Oil	687	577	110
Saline	626	495	131
Nil	62	48	14

For the purposes of the trial, affected children have been divided into four groups, as shown in Table 3. Group I are those presenting with the full syndrome of hearing or speech abnormality, abnormality of motor development and strabismus (Fig. 1).

Table 3. Classification of defective children in relation to administration of iodized oil

GROUP	TREATED			UNTREATED		
	Total	Conception		Total	Conception	
	Before Trial	After Trial	After Trial	Before Trial	After Trial	After Trial
I	3	2	1	18	3	15
II	3	3	0	13	2	11
III	2	2	0	4	2	2
IV	1	1	0	1	0	1

Group II includes those with abnormalities of hearing or speech and motor development (Fig. 2). Group III includes those with a hearing or speech defect only. Group IV includes those with motor retardation with an abnormal gait.



Figure 1. Patient classified as Group I in Table 3
 Figure 2. Patient classified as Group II in Table 3.

An appendix is attached in which a brief resume of the history and clinical features of each affected child is given.

The lack of consensus on the definition of endemic cretinism gives rise to some difficulty in assessing the results of the trial. If, for epidemiological purposes, those patients in Groups I and II can be considered endemic cretins, then there have been six cretins born to women who have had iodized oil out of a total 687 children; in five of these six cases, conception had occurred prior to the iodized oil injection. In the sixth case, the mother received the injection on October 6, 1966 and the birth-date of the infant is recorded at August, 1967, i.e. approximately 42-46 weeks later. However, the lack of precision regarding the birth-date raises the possibility that conception had occurred prior to treatment in this instance also.

In the untreated group there have been 31 endemic cretins out of a total 688 children born since that trial commenced. In five of these 33, conception had occurred prior to the saline being given. It is concluded that the neurological syndrome of endemic cretinism has occurred in the untreated group and in six instances in the treated group in five of which conception had already occurred at the time of injection.

DISCUSSION

A number of authors have drawn attention to the possibility that McCarrison's (22) "nervous" type of endemic cretinism is a congenital defect. McCullagh (23) went so far as to call the syndrome "Goiter-associated congenital defect". Eggenberger and Messerli (3) stated that the deaf-mutism has its origin in the fourth month of fetal life although no evidence is presented for this statement. Costa *et al.* (15) remarked that endemic cretinism seems to develop during intra-uterine life.

The trial of iodized oil as a prophylactic measure against endemic cretinism described here lends support to the view that the neurological damage of endemic cretinism is an intra-uterine event possibly occurring during the first trimester of pregnancy. In this time relationship it resembles the defect produced by maternal rubella infection, and it is perhaps significant that deaf-mutism is common to both syndromes. It may be that the developing auditory apparatus is peculiarly susceptible to damage during this particular period.

Evidently administration of iodine as a depot injection is effective in preventing this damage, but how iodine exerts its prophylactic effect is not clearly understood. The view most widely

held is that iodine deficiency leads to maternal hypothyroidism which is responsible for the fetal damage (24, 25), yet the evidence for this is not at all convincing. Clinical hypothyroidism is rarely seen in an endemic goiter area, and the fecundity precludes hypothyroidism of any magnitude since it is uncommon for a hypothyroid female to become pregnant. Table 1 discloses that the number of infants born to the oil injected group was not significantly different from the number born to the group that did not receive iodine. It has been suggested that subclinical biochemical hypothyroidism might exist in these women. Support for this comes from those studies reporting high serum TSH levels (26) and low serum PBI or serum thyroxine levels in some areas where iodine deficiency is severe (27, 28). It is possible therefore that a subclinical maternal hypothyroidism during a critical stage of fetal development leads to neurological damage to the fetus. This postulate seems not convincing because cases have been recorded of clinically hypothyroid women becoming pregnant and being delivered of normal children. The report by Hodges *et al.* (29) describe a woman with juvenile myxedema who had six pregnancies from which four infants survived. These four infants included a moron unable to talk at the age of four years nine months, a normal child, a mongolian idiot, and the fourth only seven months old when assessed which appeared normal. Only the first of these could possibly be said to resemble the syndrome of endemic cretinism. Lister and Ashe (30) reported a patient with myxedema untreated during the first four months of gestation who delivered a normal child.

Fetal hypothyroidism secondary to insufficient iodine is also postulated as the cause of endemic cretinism (31). However, congenitally athyreotic infants do not have the clinical features of endemic cretinism. Furthermore, there is a considerable body of evidence indicating that the human fetal thyroid commences functioning at about the 12th or 13th week of gestation whereas the damage characteristic of endemic cretinism appears from our epidemiologic observations possibly to occur before this time (32, 33).

If neither maternal nor fetal hypothyroidism can adequately account for the syndrome of endemic cretinism, how does iodine administration effectively prevent the disease? It is of course possible that a mild degree of maternal hypothyroidism coupled with fetal hypothyroidism resulting from severe iodine deficiency may be sufficient to cause the syndrome. It is also possible that elemental iodine, apart from its role in thyroid hormone synthesis, may be necessary for fetal neurological development. In this context it is perhaps significant that the mammalian ovary

concentrates iodine in the developing ovum (34). If this is so, can an iodine deficiency lead to damage in the developing ovum?

It is possible that iodine plays a secondary role, acting in conjunction with other factors, such as protein-calorie malnutrition. Maternal protein-calorie malnutrition during pregnancy has been postulated to be a cause of intellectual retardation in infants (35), and this has been supported by work on experimental animals (36). Other elements or trace elements may also influence the role of iodine. For example, the goiter rate in iodine deficient areas is influenced by the hardness of water supplies (9), possibly calcium interacts with iodine to cause endemic cretinism. An analogous situation occurs in sheep and cattle when a copper-molybdenum imbalance during pregnancy produces an irreversible neurological disorder in the calves and lambs (37).

SUMMARY

A controlled trial using a single depot injection of iodized oil as a prophylactic for endemic cretinism is described.

In the oil injected group six cretins were found among a total of 687 children born since the trial commenced; in five of these six cretins conception had occurred prior to the injection. The control group had 31 cretins among a total 688 children, with five of the 31 pregnant prior to the trial starting.

The injection is effective in preventing the syndrome, provided it is given prior to conception. This suggests that the irreversible neurological damage characteristic of the endemic cretin occurs prior to birth, possibly during the first trimester of pregnancy.

The mode of action of iodine in preventing the syndrome is discussed and in particular the view currently held, that maternal hypothyroidism is responsible for the fetal damage, is challenged.

ACKNOWLEDGEMENT

Supported by the Department of Public Health, Papua, New Guinea.

DISCUSSION BY PARTICIPANTS

FIERRO: How sure were you of the identification of these people?

PHAROAH: Very rarely were there any problems. About twenty children whose mothers came from another village have been excluded from the trial because I am not sure whether or not they have had iodine.

KOENIG: Having observed four children born to hypothyroid mothers, I looked at the literature on that subject. I found 74 women with 110 pregnancies. There were 49 normal children, 30 miscarriages or stillbirths, and 28 abnormal children. Among these 28 were six having congenital hypothyroidism. These six were two kindreds of three children each, from two families with inborn errors of metabolism. Other abnormalities among the 28 were developmental anomalies like anencephaly, spina bifida, and such things; and a single oligophrenic with no further classification. So among these 110 children there was no anomaly which was comparable to endemic cretinism. With the exception of the six patients with congenital hypothyroidism none of the children were hypothyroid (38).

ROSMAN: Regarding the question of whether malnutrition produces mental retardation, there is at least one rather convincing controlled study of Stoch and Smythe (35,39) indicating that it does. Malnourished children showed greatest impairment in weight, less in height, and least but nonetheless definite impairment in head growth and intelligence. The many malnourished children that we see at Boston City Hospital usually show the same picture, with a head circumference that tends to be at about the third percentile. In children seen at the Boston City Hospital, malnutrition is probably the most common cause of mild microcephaly and developmental retardation.

PHAROAH: Do they present with deaf-mutism, squint, and spastic diplegia?

ROSMAN: They may have an ataxic diplegia or spastic diplegia.

DELANGE: Do you have biochemical studies of thyroid function in the newborn defectives, to see if there was hypothyroidism during pregnancy?

PHAROAH: I have serum waiting to be done, but do not have the results yet.

IBBERTSON: As to hypothyroidism in the fetal environment, there is little evidence that maternal thyroxine crosses the placenta during the crucial period for nervous tissue development. The

fact that the Zaire cretin does not show neurological abnormality is strong evidence against fetal hypothyroidism being important in the genesis of neurological defects.

KROC: Would a study comparing thyroid hormone, e.g., USP desiccated or thyroxine, be feasible and desirable? Throughout these sessions there has been an implication that iodized oil treatment is equivalent to what would be observed if T₄ or T₄ plus T₃ were administered. Is there evidence from a controlled study to support that? What about any extrathyroidal effects of iodine in development of the nervous system?

IBBERTSON: In iodine-deficient areas where iodine supplementation has been given, previously low serum thyroxine levels rise to normal, making it difficult to distinguish between the effects of thyroid hormone and elemental iodine per se.

BUTTFIELD: More important is that iodine supplements drop the TSH level down to normal, so I think you can equate the two.

PRETELL: I will show this afternoon that 48 hours after one gives iodine, T₄ increases.

STANBURY: When you give iodine to the African cretins with their damaged thyroids do their PBI's go back to normal?

DELANGE: We do not know.

ERMANS: Considering the fact that the hypothyroid cretin has a very small thyroid iodine pool, we are afraid that the administration of large amounts of iodine to these patients would block the organification by a Wolff-Chaikoff effect. This could lead to an aggravation of their thyroid insufficiency.

PRETELL: Does this happen even if TSH is high?

ERMANS: No.

BUTTFIELD: Would this not be a temporary effect? If one gives thyroxine for two or three months, then the iodized oil ought to be effective, because the subject would have a high iodine uptake.

QUERIDO: I have been considering the coincidence of hearing defect and thyroid defect in the Pendred syndrome. I wondered if it is not an enzyme defect or protein defect that is also localized in other tissues than the thyroid. If so, it could be in the placental cells. If the placenta not only transports iodide but also modifies it to an unknown compound, a defect in this mechanism could have the same effect as an insufficient supply of iodide, as is the case

in endemic cretinism. This is of course highly speculative, because there are no data which indicate that the placenta metabolizes iodide.

REFERENCES

1. Marine, D. and Kimball, O.P.: Prevention of simple goiter in man. Fourth paper. Arch. Intern. Med. 25:661-672, 1920.
2. Brush, B.E. and Altland, J.K.: Goiter prevention with iodized salt: results of a thirty-year study. J. Clin. Endocrinol. Metab. 12:1380-1388, 1952.
3. Eggenberger, H. and Messerli, F.M.: Theory and results of prophylaxis of endemic goiter in Switzerland. In: Transactions of the Third International Goiter Conference, 1938. pp. 64-67.
4. Gezondheidsorganisatie, T.N.O.: De endemische Krop in Nederland, 1959.
5. McGullagh, S.F.: The Huon Peninsula endemic: I. the effectiveness of an intramuscular depot of iodized oil in the control of endemic goitre. Med. J. Aust. 1:769-777, 1963.
6. Buttfeld, I.H., Black, M.L., Hoffmann, M.J., Mason, E.K. and Hetzel, B.S.: Correction of iodine deficiency in New Guinea natives by iodised oil injection. Lancet 2:767-769, 1965.
7. Pretell, E.A., Moncloa, F., Salinas, R., Kawano, A., Guerra-Garcia, R., Gutierrez, L., Beteta, L., Pretell, J. and Wan, M.: Prophylaxis and treatment of endemic goiter in Peru with iodized oil. J. Clin. Endocrinol. Metab. 29: 1586-1595, 1969.

8. Clements, F.W.: Naturally occurring goitrogens. Br. Med. Bull. 16:133-137, 1960.
9. Taylor, S.: Calcium as a goitrogen. J. Clin. Endocrinol. Metab. 14:1412-1422, 1954.
10. Stott, H., Bhatia, B.B., Lal, R.S. and Rai, K.C.: The distribution and cause of endemic goitre in the United Provinces. Indian J. Med. Res. 18:1059-1086, 1931.
11. McCarrison, R.: Observations on endemic goitre in the Chitral and Gilgit Valleys. Lancet 1:1110-1111, 1906.
12. Report of the Pan American Health Organization Scientific Group on Research in Endemic Goiter. Pan American Health Organization Advisory Committee of Medical Research, PAHO, Washington, 1963.
13. Wespi, H.J.: Abnahme der Taubstummheit in der Schweiz als Folge der Kropfprophylaxe mit jodiertem Kochsalz. Schweiz. Med. Wochenschr. 75:625-629, 1945.
14. Buttfield, I.H. and Hetzel, B.S.: Endemic cretinism in eastern New Guinea. Australas. Ann. Med. 18:217-221, 1969.
15. Costa, A., Cottino, F., Mortara, M. and Vogliazzo, U.: Endemic cretinism in Piedmont. Panminerva Med. 6:250-259, 1964.
16. Greenwald, I.: The history of goiter in the Inca Empire: Peru, Chile and the Argentine Republic. Its significance for the etiology of the disease. Tex. Rep. Biol. Med. 15: 874-889, 1957.
17. Koenig, M.P. and Veraguth, P.: Studies of thyroid function in endemic cretins. In: Advances in Thyroid Research (R. Pitt-Rivers, ed.), Pergamon Press, Oxford, 1961. pp. 294-300.
18. Norris, H.: Notice of a remarkable disease analogous to cretinism existing in a small village in the west of England. Med. Times 17:257-258, 1847-48.
19. Fagge, C.H.: Sporadic cretinism occurring in England. Medico-chir. Trans. 54:155-170, 1871.
20. Trotter, W.R.: The association of deafness with thyroid dysfunction. Br. Med. Bull. 16:92-98, 1960.

21. Pharoah, P.O.D., Buttfeld, I.H., and Hetzel, B.S.: Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. Lancet 1:308-310, 1971.
22. McCarrison, R.: Observations on endemic cretinism in the Chitral and Gilgit Valleys. Lancet 2:1275-1280, 1908.
23. McCullagh, S.F.: The Huon Peninsula endemic: IV. Endemic goitre and congenital defect. Med. J. Aust. 1:884-890, 1963.
24. Stanbury, J.B.: Endemic Goiter. In: Clinical Endocrinology II (Cassidy and E.B. Astwood, eds.), New York, Grune & Stratton, 1968. pp. 195-209.
25. Querido, A.: Endemic cretinism: a search for a tenable definition. In: Endemic Goiter. Report of the meeting of the PAHO Scientific Group on Research in Endemic Goiter held in Mexico, 1968. (J.B. Stanbury, ed.), Scientific Publication No. 193, Washington, 1969. pp. 85-89.
26. Adams, D.D., Kennedy, T.H., Choufoer, J.C., Querido, A.: Endemic goiter in western New Guinea. III. Thyroid-stimulating activity of serum from severely iodine-deficient people. J. Clin. Endocrinol. Metab. 28:685-692, 1968.
27. Raman, G. and Beierwaltes, W.H.: Correlation of goiter, deafmutism and mental retardation with serum thyroid hormone levels in non-cretinous inhabitants of a severe endemic goiter area in India. J. Clin. Endocrinol. Metab. 19: 228-233, 1959.
28. Choufoer, J.C., Van Rhijn, M., Kassenaar, A.A.H. and Querido, A.: Endemic goiter in western New Guinea: iodine metabolism in goitrous and nongoitrous subjects. J. Clin. Endocrinol. Metab 23:1203-1217, 1963.
29. Hodges, R.E., Hamilton, H.E., and Keettel, W.C.: Pregnancy in Myxedema. A.M.A. Arch. Int. Med. 90:863-868, 1952.
30. Lister, L.M. and Ashe, J.R.: Pregnancy and myxedema. Report of a case. Obstet. Gynecol. 6:436-441, 1955.
31. Choufoer, J.C., Van Rhijn, M. and Querido, A.: Endemic goiter in western New Guinea. II. Clinical picture, incidence and pathogenesis of endemic cretinism. J. Clin. Endocrinol. Metab. 25: 385-402, 1965.

32. Chapman, E.M., Corner, G.W., Robinson, D. and Evans, R.D.: The collection of radioactive iodine by the human fetal thyroid. J. Clin. Endocrinol. Metab. 8:717-720, 1948.
33. Costa, A., Cottino, F., Dellepiane, M., Ferraris, G.M., Lenart, L., Magro, G., Patrino, G., Zoppetti, G.: Thyroid function and thyrotropin activity in mother and fetus. In: Current Topics in Thyroid Research (C. Cassano and M. Andreoli, eds), Academic Press, New York, 1965. pp. 738-748.
34. Brown-Grant, K.: Extrathyroidal iodide concentrating mechanisms. Physiol. Rev. 41:189-213, 1961.
35. Stoch, M.B. and Smythe, P.M.: Does undernutrition during infancy inhibit brain growth and subsequent intellectual development? Arch. Dis. Child. 38:546-552, 1963.
36. Winick, M., Fish, I. and Rosso, P.: Cellular recovery in rat tissues after a brief period of neonatal malnutrition. J. Nutr. 95:623-626, 1968.
37. Underwood, E.J.: The mineral nutrition of livestock. Published by arrangement with the Food and Agriculture Organization of the United Nations by Commonwealth Agricultural Bureau, 1966. pp. 120-146.
38. Koenig, M.P.: Die kongenitale Hypothyreose und der endemische Kretinismus. Springer, Berlin, 1968.
39. Stoch, M.B. and Smythe, P.M.: The effect of undernutrition during infancy on subsequent brain growth and intellectual development. S. Afr. Med. J. 41:1027-1030, 1967.

APPENDIX

*GROUP I: ABNORMALITIES OF HEARING AND/OR SPEECH,
ABNORMALITIES OF MOTOR DEVELOPMENT AND SQUINT**Oil*

Case 1. Mother approximately 32 weeks pregnant at time of oil injection. Female infant, last seen when aged four years eight months, is deaf and mute, mentally defective, has an upper motor neuron lesion involving arms and legs with extensor plantars responses and is unable to sit unsupported.

Case 2. Mother injected October 6, 1966. Female infant born August, 1967 and died October, 1970. At age three years eight months was unable to sit or crawl, the limbs being hypotonic. The child was deaf and mute and had an internal strabismus.

Case 3. Male born January, 1967. Mother approximately 26 weeks pregnant when injected with oil. Walking delayed until three years of age. Last examined aged four years four months; the gait is abnormal and mother states the child is not talking but claims the child can hear. Clinically he does not appear to hear a tuning fork, he is probably partially deaf. There is an intermittent squinting of either eye.

Saline

Case 1. Male born November 4, 1967. Is deaf, mute and has a transient inward and upward squinting of either eye. Commenced walking sometime after three years four months of age. Gait is abnormal, the plantar responses are extensor and 4 or 5 beats of ankle clonus can be elicited.

Case 2. Female born January 30, 1969. At age two years 11 months has a severe head lag when pulled to the sitting position and is unable to sit unsupported. She is deaf and mute and severely mentally defective. The tendon reflexes in the arms and legs are pathologically brisk and there is an internal strabismus.

Case 3. Female born September 26, 1968. At age two years eight months is unable to sit unsupported, is deaf and mute, has a severe strabismus involving both eyes and extensor plantar responses.

Case 4. Male born June 13, 1969. At age two years five months is unable to sit, has a severe squint, is grossly mentally retarded and is a deaf-mute. The tendon reflexes in both arms

and legs are excessively brisk and the plantar reflex is extensor.

Case 5. Male born February 5, 1968. Unable to sit up until over two years of age and when last examined aged three years nine months was unable to walk; is a mentally retarded deaf-mute and has a transient squinting of either eye.

Case 6. Male born March 24, 1970. At 12 months was unable to sit and there was considerable head lag when pulled from lying supine to the sitting position. At 18 months the child can sit but has a very rounded back. He shows a squint and has no speech. The parents state the child is deaf.

Case 7. Male born September 18, 1969. Was unable to sit at age 14 months but had attained this milestone by age 19 months. At age two years two months is unable to stand or walk and has extensor plantar responses; the child is deaf, mute and has an intermittent strabismus.

Case 8. Male born November 15, 1967. A severely affected mentally defective, squinting deaf-mute who is unable to walk at four years of age.

Case 9. Male born September 14, 1968. At one year seven months was unable to sit upright. When last seen age three years, he was almost able to walk. The mother states that speech is not normal though at least partial hearing is present as he can hear a finger snap. There is an inward squinting of the left eye.

Case 10. Male born December, 1966, mother approximately 30 weeks pregnant at time of saline injection. The child was first seen age three years four months when walking was established though the gait was unsteady and wide-based with flexed knees and hips. At four years 11 months he is mute though partial hearing at least is present and there is an internal strabismus of the left eye.

Case 11. Male born April 10, 1968. A deaf-mute with a squint and spasticity of the legs, pathologically brisk knee and ankle jerks and extensor plantar responses. At three years eight months of age he is still unable to sit unsupported.

Case 12. Male born March 19, 1967. Mother was approximately 16 weeks pregnant at time of saline injection. The child started sitting sometime after three years of age and walking commenced between the ages of four years and four years nine months. The gait is grossly abnormal; there is a severe strabismus and he is a deaf-mute.

Case 13. Male born December, 1967. At age three years six months is just able to sit unaided but cannot stand or walk. He is deaf-mute and has a strabismus.

Case 14. Male born May 28, 1968. Died aged two years two months. Last examined when aged one year 11 months; he was deaf and had no speech; was only able to stand if supported and had an internal strabismus.

Case 15. Male born February, 1967, died aged three years nine months. A severely affected child who was unable to sit aged three; was deaf and mute and had a squint. Mother was approximately 24 weeks pregnant at time of saline injection.

Case 16. Male born October, 1968. Sitting not attained until over 13 months of age and walking at about two years, though the gait at this time was very unsteady. He has a pronounced squint of the left eye. The parents state he hears if they call in a loud voice but that speech is not normal.

Case 17. Male born April 29, 1970. Is as yet unable to sit upright or crawl aged 18 months; has marked transient squinting of either eye and does not hear a finger snap.

Case 18. Female born January, 1970. Was unable to sit until after 15 months of age and when last examined aged one year 10 months was unable to stand or walk. She has a transient squinting of either eye, is not yet talking and does not hear a finger snap.

*GROUP II: ABNORMALITIES OF HEARING AND/OR SPEECH AND
MOTOR DEVELOPMENT*

Oil

Case 1. Female born December 13, 1966. Mother approximately 30 weeks pregnant at time of oil injection. Sitting was delayed until after three years of age and walking until about four years. The gait at four years nine months is abnormal, and the child is deaf and mute.

Case 2. Male born November 7, 1966. Mother approximately 34 weeks pregnant at time of oil injection. A mentally defective child who at four years 10 months has spasticity of the lower limbs with pathologically brisk reflexes and extensor plantar responses and is unable to walk or stand. He is also deaf-mute.

Case 3. Female born May 4, 1967, died aged three years seven months. At the time of death was yet unable to sit and was a deaf-mute. Mother was approximately 13 weeks pregnant at time of oil injection.

Saline

Case 1. Male born March 13, 1968. Began sitting at about one year eleven months and walking at three years. Gait is very unsteady and spastic. Is also deaf-mute.

Case 2. Male born November 16, 1968. Is mute but at least partial hearing is present. Began sitting at one year three months and walking at two years five months but gait is abnormal.

Case 3. Male born July, 1967. Commenced walking when aged three years nine months but gait is unsteady and spastic and knee and ankle jerks are pathologically brisk. Is also deaf and mute.

Case 4. Male born December 9, 1968. Is deaf and mute. Sitting commenced sometime after the age of two. The left ankle and knee are fixed due to scarring from a burn which partly accounts for the inability to walk, nevertheless the tendon reflexes in the right leg are pathologically brisk.

Case 5. Female born April, 1967. Mother approximately 10 weeks pregnant when injected with saline. Child first seen when aged two years seven months when walking was established but gait appeared abnormal; the tendon reflexes excessively brisk and the plantar responses are extensor. She is mute and conveys requests to her mother by means of signs though she does not appear to be deaf.

Case 6. Male born October, 1969. Sitting not achieved until after 13 months. Last examined aged two years one month. He is unable to stand or walk and when sitting there is a marked kyphosis of the back. He has no speech and there is at least a partial hearing loss.

Case 7. Female born November 7, 1968. Deaf and mute; sitting not achieved until after two years and is still unable to stand or walk at two years ten months.

Case 8. Female born April 15, 1969. Is mute but has at least partial hearing. Walking commenced aged three years and when last examined aged three years eight months, gait is unsteady, stiff with flexed knees and hips.

Case 9. Male born February 21, 1968. Deaf and mute. Sitting commenced aged two and walking sometime after three years of age. The gait is wide based and stiff.

Case 10. Male born November, 1966. Mother approximately 32 weeks pregnant at time of saline injection. The child was first seen when aged three. He could walk but the gait was broad based, unsteady and stamping. The mother complained of the child's inability to talk and this remains the major complaint, though hearing appears fairly normal.

Case 11. Male born February 10, 1968. Commenced walking aged about three years two months. Gait is stamping, unsteady and spastic. At the last examination when aged three years nine months, the parents state the child's speech is not normal, but claim that hearing is all right.

Case 12. Male born December 6, 1969. Last examined aged 13 months, and is unable to sit upright and legs are spastic. There is no response to a tuning fork or handclap.

Case 13. Female born February 26, 1969. Sitting commenced after the age of 14 months. When last examined aged two years 10 months, she is unable to walk and crawling is most ineffective and spastic. The mother says the child is not talking properly though she can hear and this is confirmed by the child's ability to hear a tuning fork.

GROUP III: ABNORMALITIES OF HEARING AND/OR SPEECH ONLY

Oil

Case 1. Male born January 15, 1967. Mother had oil injection when approximately 24 weeks pregnant. Parents state that the child does not talk at all although hearing is essentially normal. There has been no evidence of any motor retardation.

Case 2. Male born January 15, 1967. Mother had oil injection when approximately 24 weeks pregnant. When last examined aged four years ten months his parents state he is not talking at all but hearing is normal. He can undoubtedly hear a tuning fork.

Saline

Case 1. Male born March 5, 1967. Mother injected with saline when approximately 18 weeks pregnant. First seen when aged two years eight months; walking was established and the gait was normal. He is unable to talk and is deaf and this is confirmed by the fact that communication with the child is by signs.

Case 2. Male born March, 1967. Mother injected with saline when approximately 18 weeks pregnant. He is unable to talk and is at least partially deaf, when last examined aged four years two months.

Case 3. Male born July 21, 1967. Mute and partially deaf. Motor milestones were normal.

Case 4. Male born March 24, 1968. When last examined aged two years eight months, the parents complained that speech is not normal, though there does not appear to be any hearing loss. Commenced walking at about 23 months.

GROUP IV: MOTOR RETARDATION WITH AN ABNORMAL GAIT

Oil

Case 1. Male born December, 1966. Mother approximately 30 weeks pregnant when injected with oil. Motor milestones retarded; was unable to sit unsupported until over age one year and did not walk until nearly three years. Gait is abnormal and speech was retarded. When the child was aged three, the parents complained that speech was not normal although when last seen, aged five years, it was stated that the child's speech was normal and there is no gross hearing loss.

Saline

Case 1. Female born October 20, 1967. Did not commence walking until over three years of age. Gait is abnormal with flexed knees and hips and very unsteady so that the child tends to fall after every one or two steps. At three years six months, the child is able to sit but there is a marked kyphosis of the spine. There does not appear to be any deficit of speech or hearing.