

A Controlled Trial of Iodinated Oil for the Prevention of Endemic Cretinism: A Long-Term Follow-Up

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A double blind controlled trial designed to examine the effectiveness of intramuscular iodinated oil as a prophylactic for the nervous type of endemic cretinism was begun in 1966 in the highlands of Papua New Guinea. Infants born into the trial between 1966 and 1972 were followed up until 1982. The results showed that if the iodine supplement was given before conception the nervous form of endemic cretinism was prevented. Also a striking difference in the 15-year cumulative survival rate in favour of the test (iodinated oil) group was observed. Measures of motor and intellectual function revealed that children born to mothers given an iodine supplement performed significantly better. This observation shows that iodine deficiency leads to sub-clinical as well as clinical deficits. It also justifies the use of the term iodine deficiency disorder to cover the polymorphic nature of the abnormalities attributable to iodine deficiency.

The original classification of endemic cretinism into two types, the 'nervous' and the 'myxoedematous', was made by McCarrison in 1908.¹ For 50 years there was continuing controversy over the definition of the syndrome, which culminated in the Pan American Health Organization definition.² The PAHO definition states that the clinical manifestations comprise mental deficiency together with either; (a) a predominant neurological syndrome consisting of defects of hearing and speech and with characteristic disorders of stance and gait of varying degrees, or (b) predominant hypothyroidism and stunted growth. The wheel it seems has come full circle and the new definition vindicates McCarrison's original classification. The relative proportions of the two subtypes of endemic cretinism vary in different parts of the world. The hypothyroid variety appears to predominate in some African countries, while the nervous variety is more common in most other countries.^{3,4} In Papua New Guinea the neurological type of endemic cretinism predominates.

In an attempt to resolve the controversy surrounding the role of iodine deficiency in the aetiology of cretinism a double-blind controlled trial using intramuscular iodinated oil was started in the Jimi valley of the

Western Highlands Province of Papua New Guinea in 1966 and completed in 1972.^{5,6} A high prevalence of goitre and an increased thyroidal radio ¹³¹I uptake indicated that iodine deficiency was a significant problem in the area. At this stage the diagnosis of endemic cretinism was based on evidence of deafness or strabismus and developmental delay as indicated by the relatively crude assessments provided by motor milestones, such as the age at which children achieved independent sitting, standing and walking.

This paper presents the final follow-up results on the children born between 1966 and 1972. The children were last examined in 1982 when they were aged between 10 and 16 years.

MATERIALS AND METHODS

Setting up the controlled trial, the diagnosis of cretinism and the early follow-up have been described previously.^{5,6} Goitre grading was carried out using the criteria specified by Perez, Munoz and Scrimshaw.⁷ During 1970 and 1971 blood samples were taken from pregnant women and the serum frozen as soon as possible after collection, and in all cases within 36 hours. The methods of analysis for serum total thyroxine (TT₄) and serum thyroid binding globulin (TBG) have been described previously.⁸

The trial was ended in 1972 when iodinated oil injections were given to all women of child bearing age in

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each of the villages. Since 1972 the follow-up of the children in the trial has been limited to five of the original 13 villages which had the highest prevalence of cretinism ranging from 29.3 to 33.3 per 1000 total population. The decision to limit further follow-up to five of the 13 villages was made for logistical reasons. The area in which the villages lie is rugged, mountainous country with no roads and the only means of visiting villages is on foot. In order to spend more time in examining and assessing each child it was necessary to reduce the area covered.

The cohort of children born into the trial in the five villages was further examined in 1974, 1976, 1978 and 1982, particular attention being given to abnormalities of speech and hearing and signs of upper motor neurone lesions in those children who were developmentally delayed. In 1978 and 1982 measures of cognitive and motor performance were incorporated into the assessment schedule. A definite cretin was so designated if there were abnormalities of hearing and/or speech together with evidence of an upper motor neurone lesion. Possible cretins included those who had hearing and/or speech abnormalities but in whom there was no clinical evidence of an upper motor neurone lesion, although in most cases motor milestones were also delayed. A note was made of all the children who had died. In the majority of cases it was not possible to obtain the precise date of death and, for the purpose of constructing survival curves, the midpoint between the date when the child was last seen alive and the date when death was noted was taken to be the date of death. The people of the Jimi valley do not have a written language, and measures of time are less important than in Western society, consequently the people themselves usually have no accurate record of when a death occurred.

From the range of tests applied in 1978 two were found to discriminate well for motor performance.⁹ Both these tests measured manual dexterity. The first required the use of both hands working together in collaboration and involved threading beads onto a lace. The beads were approximately $\frac{1}{8}$ inch external diameter, one end of the lace was knotted and the other wrapped to give a stiff, one and a half inch section. The test period was 60 seconds and the task to thread as many beads as possible. The child's score for the test was the number of beads he succeeded in threading during the one minute period. At the end of the trial the child was allowed to keep the lace and beads which he had threaded. These are valued as decorative items and served as a great incentive to the children. The second task, which also demanded accuracy, was carried out with one hand. The child was

required to insert as many pegs as possible in a pegboard. The pegboard was six and a half inches square and contained 100 equally spaced holes. A box containing a large number of mushroom shaped pegs, $\frac{1}{4}$ inch diameter at the top, which fitted easily into the holes, was placed by the side of the pegboard. The child was instructed to insert pegs into the board as quickly as possible and the score obtained was the number of pegs which could be fitted in 60 seconds. The requirements of these tests were demonstrated to the children and they were given two or three practice trials to ensure that they understood what was required of them. The demonstration was also supplemented by simple verbal instructions in pidgin English.

In 1982 the pegboard and bead threading tests were repeated. In addition an attempt was made to assess the intellectual performance of the children using the Pacific Design Construction Test (PDCT) developed by Ord and used in Papua New Guinea to select army recruits and young people for technical training.¹⁰ The test is made up of 13 designs of varying complexity printed on cards. The subject is shown a printed card containing the design and asked to make a copy of it in tiles (red, white and red/white) in a set of specially shaped trays. An initial test carried out on children from the study area, children who were not themselves part of the trial cohort, showed that they experienced great difficulty in translating the printed design into a model made from tiles. The procedure was therefore modified. The examiner constructed the design in tiles in one tray whilst the subject watched. The subject was then invited to reproduce the design in an adjacent tray. The model was available to the subject throughout the trial. The test was administered in a manner which relied largely on non-verbal instructions, though these were supplemented by verbal instructions translated into pidgin English for use in the field. The details are given in Pharoah *et al.*¹¹

RESULTS

Table 1 shows the age and sex-specific goitre rates in test and control groups. There is the expected difference in goitre rates between males and females but no significant difference in male or female goitre rates between the test and the control groups.

In addition to the raised goitre rates, confirmation that iodine deficiency was severe was obtained from the serum TT_4 values observed among pregnant women in the control group who had not received supplementary iodine. Fifty per cent of these women had serum TT_4 levels below the lower limit of normal (60 ng/ml) on UK samples and some had exceedingly low values. In contrast all the women who had received

TABLE 1 Age and sex-specific goitre rates (%) in test (oil) and control (saline) groups.

Goitre grade	Males									
	0-9 yrs		10-19 yrs		20-39 yrs		40+ yrs		All ages	
	Oil n = 124	Saline n = 112	Oil n = 201	Saline n = 167	Oil n = 183	Saline n = 172	Oil n = 101	Saline n = 102	Oil n = 610	Saline n = 553
0	94.4	92.0	81.1	80.2	92.9	95.3	97.0	98.0	90.0	90.6
1	5.6	8.0	11.9	13.8	2.7	1.2	1.0	2.0	6.1	6.5
2	0.0	0.0	7.9	6.0	4.4	3.5	2.0	0.0	3.9	2.9

Goitre grade	Females									
	Oil n = 125	Saline n = 136	Oil n = 145	Saline n = 162	Oil n = 209	Saline n = 200	Oil n = 112	Saline n = 90	Oil n = 594	Saline n = 591
	0	90.4	89.7	60.0	59.3	60.8	67.0	79.5	84.4	70.5
1	8.0	6.6	17.9	17.3	8.6	13.0	8.9	6.7	10.8	12.0
2	1.6	3.7	22.1	23.5	30.6	20.0	11.6	8.9	18.7	15.4

supplementary iodine had serum TT_4 levels within the normal range even after the lapse of 4-5 years from the time of injection (Table 2). There was no significant difference in the serum TBG between the test and control groups so that the observed differences in serum TT_4 values were not attributable to a difference in the level of binding globulins.

Mortality

The cumulative survival curves of children from the oil and saline groups up to 1982 are shown in Figure 1. The 15 years cumulative survival of the children whose mothers received supplementary iodine is significantly greater than the control children ($p = 0.002$, Lee-Desu statistic, SPSS). Unfortunately information on the cause of death in each individual case could not be obtained.

Incidence of Cretinism

Assessment of the trial results up to 1972 has previously been reported.^{5,6} However, the criteria employed in defining endemic cretinism were rela-

tively crude. They involved deafness, and/or the presence of a squint, along with a delay in the attainment of the motor milestones of independent sitting, standing and walking. The later follow-up in 1982, which was carried out in five of the original 13 villages, and which involved more detailed clinical assessment, along with quantitative measures of motor and intellectual performance, confirmed the original observations.

Out of the 274 children born into the test group (mothers given iodinated oil) 3 were definite cretins. In each of these cases the mother had received iodinated oil after conception; at 30, 32 and 34 weeks gestation respectively. There were 3 possible cretins, one of whom had been conceived before the mother received iodinated oil, at 24 weeks gestation. Of the 248 children in the control group, 16 were definite cretins, the mothers of 2 of these had received the placebo injection at 16 and 30 weeks gestation respectively. There were 11 possible cretins in the control group, 2 of whom had been conceived before their mothers received the placebo injection, at 10 and 18 weeks respectively. The 10th centile was used as a cutoff point

TABLE 2 Serum total thyroxine and thyroid binding globulins (TBG) during pregnancy.

	CONTROL (saline)		TEST (iodinated oil)	
	Mean (SE)	Range	Mean (SE)	Range
Serum TT_4 ng/ml	59.8 (6.3) n = 32	5-154	128.1 (5.1) n = 20	94-167
Serum TBG μ g/ml	59.1 (2.6) n = 15	40-79	53.2 (1.8) n = 14	44-66

NB: the lower limit of the normal thyroxine level in a UK population is 60 ng/ml.

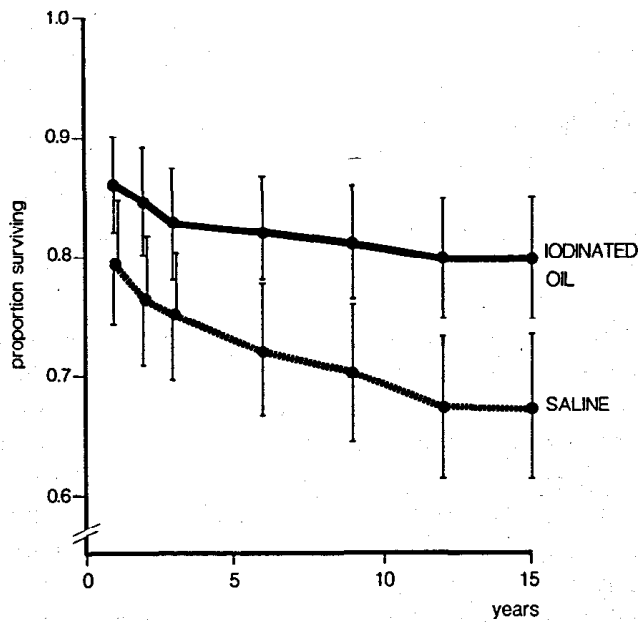


FIGURE 1 Cumulative survival rates of children whose mothers received either iodinated oil or saline (95% confidence limits).

for assessing performance on the cognitive and motor tests, all the definite cretins and all except one of the possible cretins performed poorly, ie below the 10th centile on at least one of the tests. Even after excluding the definite and possible cretins, a larger proportion of children in the control group, 17 out of 192, performed poorly compared to the test group, where it was 13 out of 235. The data are summarized in Figure 2. Analysis of the 237 test and 215 control children who were conceived after entry of the mother into the trial shows a clear and highly significant difference of 'definite' cretins, 'possible' cretins and poor performers between the test and the control groups ($\chi^2_{3DF} = 33.87$; $p < .001$).

DISCUSSION

The long-term follow-up of the controlled trial confirms the previous claim^{5,6} that the nervous variety of endemic cretinism is preventable by the provision of supplementary iodine if this is given before conception. However, there are two further important features of the results. First, there is concern about the nature and severity of damage to an infant consequent upon maternal iodine deficiency; that is to say, is the damage an 'all or none' phenomenon as exemplified by the syndrome of endemic cretinism or is there a spectrum of disorder ranging from gross pathology through subclinical deficits into normality. The widespread distribution of severe iodine deficiency in various parts of the world means that the answer to this question has widespread social implications. Our results indicate that there is a spectrum of disorder that is preventable.

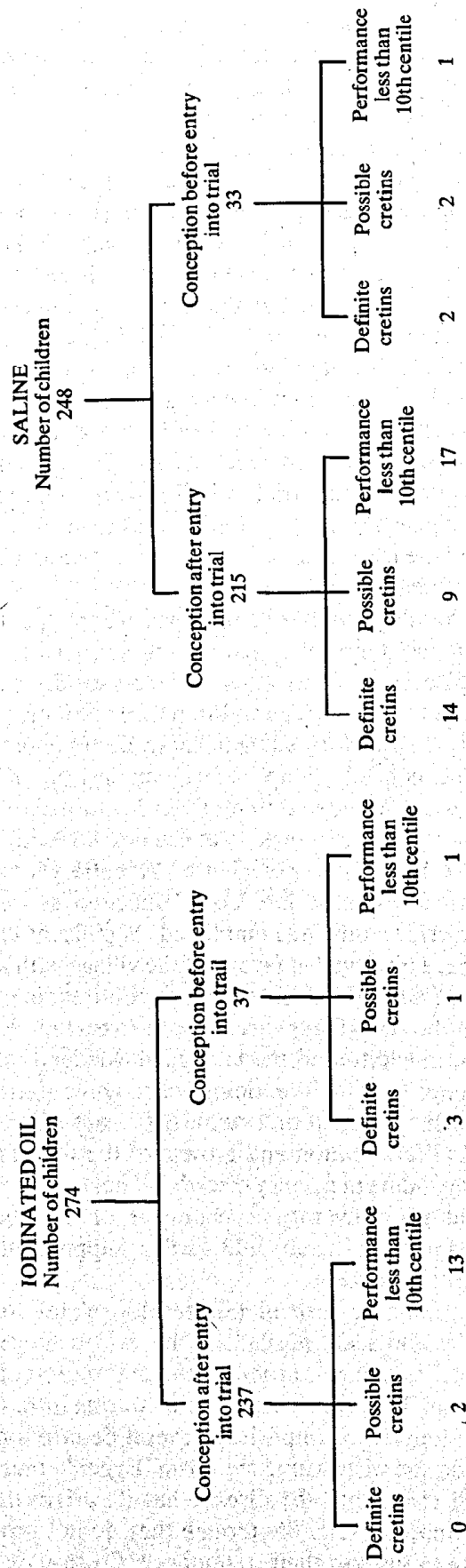


FIGURE 2

Not only is the nervous form of endemic cretinism prevented and long-term survival improved but sub-clinical deficits of intellectual and motor function, revealed by more sensitive measures, are also reduced, confirming our previous results.⁹

Similar observations have been made elsewhere. In an iodinated oil trial in Ecuador the children followed-up were aged 2-9 years and the Stanford-Binet intelligence test used.¹² A significant difference between the two groups of children (ie whose mothers had or had not received supplementary iodine) was found. However the trial was not blind, one village provided the test population and another the control. The number of children in each group was small and there were exclusions because of failure to cooperate or because the children were suffering from malnutrition. In Peru a small trial of iodinated oil found marginally higher IQs among children whose mothers had received the iodine supplement but the difference was not statistically significant.¹³

In a double-blind trial in Zaire where the myxoedematous type of cretinism predominates, the Brunet-Lezine scale was used to assess children up to the age of two years. The children from mothers in the treated group performed significantly better than those from the control group.¹⁴ The comparison of two groups was addressed differently in Java where a high goitre prevalence village was compared with one having a low goitre prevalence. A battery of tests designed to examine intellectual function as well as motor performance was employed. Significant differences were observed in favour of the village with a low goitre prevalence but the effects of confounding variables in the two villages are difficult to exclude.^{15,16}

Thus, in addition to the long acknowledged role of iodine deficiency in the aetiology of endemic goitre it is also evident that maternal iodine deficiency affects the normal differentiation and growth of the fetal brain. The term iodine deficiency disorders¹⁷ has been used to highlight the polymorphic character of the clinical effects and these results add further support for the utility of the concept.

The second feature of our results relates to the pathophysiological mechanism by which maternal iodine deficiency compromises the maturation of the fetal brain. That the damage occurs during intra-uterine development is implicit in several descriptions of the syndrome of endemic cretinism. Eggenberger and Messerli claim that the disease has its origin in the fourth month of fetal life though they do not provide evidence to support their statement.¹⁸ Costa *et al.* also claim that endemic cretinism develops during intra-uterine life¹⁹ and McCullagh called the syndrome

'goitre associated congenital defect'.²⁰ Indeed, as early as 1871, Fagge compared the syndrome of sporadic with that of endemic cretinism and concluded that sporadic cretinism was not necessarily congenital, implying that the endemic variety is.²¹ In an earlier discussion on the nature of the pathophysiological mechanism we speculated that elemental iodine, apart from its role in hormonogenesis, may be essential to early fetal brain development prior to the establishment of a functional fetal thyroid gland.⁵ This suggestion was made in the light of the generally held assumption that maternal thyroid hormones do not normally cross the placenta to the fetus. However, recent experimental work with animals throws doubt on this assumption, there is evidence of a rapid accumulation of maternal hormones in the fetus^{22,23} early in pregnancy. The essential biochemical abnormality that is found with severe iodine deficiency is a reduction in the level of serum thyroxine; triiodothyronine is usually within the normal range and is presumably responsible for maintaining clinical euthyroidism.²⁴ The finding that maternal thyroxine, but not maternal triiodothyronine, levels during pregnancy correlate with the subsequent intellectual and motor function of the child suggests that thyroxine is not merely a prohormone for triiodothyronine but that it has a specific role in pregnancy prior to the autonomous functioning of the fetal thyroid.¹¹ The data presented here are compatible with both the hypotheses and further experimental work is required to determine the pathophysiological mechanism of the neurological abnormality. However, we favour the view that iodine deficiency acts to damage the fetal nervous system via a reduction in the availability of maternal thyroxine early in gestation.

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