

## FETAL IODINE DEFICIENCY AND MOTOR PERFORMANCE DURING CHILDHOOD

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**Summary** Motor performance of children born to mothers living in an iodine-deficient region was assessed. The mothers were participants in a controlled trial of intramuscular iodised oil in the prevention of endemic cretinism carried out in the Western Highlands of Papua New Guinea. Mothers received either iodised oil or placebo saline. Children born to mothers given iodine were significantly faster and more accurate in tests of manual function than children from control mothers. The findings indicate that iodine deficiency may lead to a spectrum of subclinical deficits which place the children at a developmental disadvantage.

### Introduction

ENDEMIC cretinism is a complex syndrome associated with iodine deficiency in which neurological defects including spastic diplegia, strabismus, deaf-mutism, impairment in somatic development, and mental deficiency may be present. Deaf-mutism is the commonest feature. The condition is found where dietary iodine deficiency occurs and is associated geographically with endemic cretinism. The significance of iodine in the aetiology of the syndrome has been demonstrated by a controlled trial of intramuscular iodised oil which started in 1966 in the Western Highlands Province in Papua New Guinea. This trial demonstrated that the condition could be effectively prevented by an iodine supplement before conception.<sup>1,2</sup> The developing fetal brain is probably damaged by iodine deficiency during the first trimester. In Papua New Guinea an epidemic of cretinism coincided with the withdrawal of a major source of dietary iodine.<sup>3</sup>

Is endemic cretinism an all-or-none phenomenon or does dietary iodine deficiency result in a range of abnormality from the severe form of endemic cretinism through to subclinical conditions in which the child manifests no obvious signs but is developmentally disadvantaged in comparison with appropriate control children who have not been subject to dietary iodine deficiency during fetal life? We examined the motor performance of a cohort of children born since 1966 whose mothers had received either an intramuscular injection of iodised oil or a placebo injection of saline.

### Patients and Methods

The controlled trial was begun in the autumn of 1966 in the Jimi Valley in the Western Highlands Province of Papua New Guinea.<sup>1</sup> Alternate families in each village were injected with either iodised oil or saline, each member receiving 4 ml if over 12 years old and 2 ml if under 12. The iodised oil contained approximately 400 mg of iodine per ml. The 1978 follow-up study was confined to 5 of the villages making up the original trial. These 5 villages showed the greatest incidence of cretinism, but since alternate families in each village were allocated to treatment or control groups no bias was introduced.

Assessment of intellectual performance in primitive societies is difficult<sup>4</sup> as is evaluation of motor skills. There are no reliable standardised tests which can be applied across cultures. The tests used were selected with several constraints in mind. Since the patrol had to be completed in four-weeks and as many children as possible had to be tested, the time taken with each child was important. The tests also had to be sensitive throughout the age-range of the children tested, valid, and involve simple equipment. The language barrier is formidable therefore all the tests were of the kind that could be demonstrated non-verbally to the children, though it was possible to communicate in pidgin English with some of them.

Neither the mother nor the person administering the tests knew whether the mother had been given an iodine supplement or a saline placebo.

The tests used and the procedures were as follows:

*Grip strength* was ascertained for the left and right hands by a hand dynamometer. The size of the dynamometer was adjusted to fit the individual's hand. Grip strength was recorded to the nearest 0.5 kg.

*Speed of movement.*—Two closely similar measures were used—i.e., tapping and dotting with a pencil. The tapping task required the child to tap as rapidly as possible on a button connected via a microswitch to an electromagnetic counter which recorded the number of taps produced in 10 s. The period was timed with a stopwatch. In the second task the child was given a pencil and a pad of paper attached to a clipboard and asked to dot as quickly as possible on the instruction "go" and to cease on the command "stop". The tester gave the commands in the local language (Mareng). Four 10 s trials were given with an interval of approximately 20 s between trials. Any dots produced after the command to stop were ringed and excluded from the total. The mean number of dots produced in 10 s was used as the score. The variance between the 4 trials was very slight.

*Unimanual accuracy.*—Two tests were used. The first was the time taken to screw 9 nuts on to 9 bolts. The bolts were mounted on a 4 inch square aluminium plate with 1½ inches between their centres. The nuts (5/16 inch Whitworth, right-hand thread) were screwed on to a depth ¼ inch. The time taken to screw on all the nuts provided the child's score. The second task involved the child putting pegs into a pegboard. The pegboard was 6½ inch square with 100 holes. There was ½ inch between centres. A box containing a large number of mushroom-shaped pegs ¼ inch in diameter at the top, which fitted easily into the holes, was placed by the side of the pegboard. It was placed on the right for right-handed children and

on the left for left-handed children. The score was the number of pegs which could be fitted in 60 s.

*Bimanual accuracy.*—This task involved threading as many brightly coloured glass beads, approximately 5/16 inch external diameter, on to a knotted lace, the end of which was wrapped to give a stiff 1½ inch end, in 60 s. Both hands were needed to hold and locate the beads on the lace. At the end of the trial the child was allowed to keep the lace with the beads which had been threaded. Since beads were a valued commodity the children were highly motivated in this task.

*The test of motor impairment*<sup>5,6</sup> was based upon the Lincoln/Oseretsky<sup>7</sup> motor development scale which was devised as a screening instrument to detect motor impairment of neurological origin. At each level, in 1 year steps, 5 categories of motor function are examined: control and balance of the body while immobile, control and coordination of the arms, control and coordination of the body while in motion, manual dexterity with the emphasis on speed, simultaneous movement, and precision. The test was developed and standardised on children in the U.K. and Canada and the criteria specified proved too strict for the Jimi children. The scoring system was therefore adapted in the field and, rather than pass/fail judgements being made, the time and the number of trials required for each child was recorded. This adaptation allows some comparison to be made between the two groups.

Because communication was difficult, tests were first demonstrated to the child who was then allowed a trial before performing the test proper. This brief practice provided a means of ensuring that the child understood what was required of him. Fortunately the tasks, with the exception of some items from the test of motor impairment were simple.

Records maintained by local aid-post orderlies or mission infant welfare services provided the exact date of birth for most children. For those children for whom only the month of birth was recorded, the 15th day of the month was arbitrarily designated as the day of birth. The age of the child was determined by the number of completed months to the day that the test was administered. The conditions under which these tests were performed were not ideal; an open hut with a dirt floor or a modestly fitted mission school were used when possible. In one village the tests were carried out in the open in a small clearing. These conditions, with extraneous noise and other very curious adults and children looking on, were distracting, but conditions were similar for all children.

### Results

In the 5 villages 208 children were tested. 14 were found to be cretins and data from these children were excluded from the analysis. When the code was broken on completion of the patrol, 115 were from the treated group (iodine in oil) and 79 were from the control (saline) group. The difference in group size is explained by the higher mortality amongst the saline group<sup>8</sup> and by the fact that 13 of the 14 cretins were from the control population.

Motor performance gradually improves throughout childhood. To compare the data from the treatment and control groups and take account of age effects an analysis of covariance was performed. This revealed no difference between the groups in grip strength or in movement speed measured by tapping and dotting. Nor was there any difference between the groups for the screwing task. However, the treated group was significantly better on the speed/accuracy tests of the pegboard and bead threading,  $p < 0.05$  and  $p < 0.01$  respectively. The results from these two stringent tests, indicate that the children from the treated group were significantly better in demanding and unpracticed tasks. The results from the screwing task are at first sight surprising since this also

is a task which requires dextrous manipulation. Both groups of children found it difficult to perform, probably because this was an action totally foreign to their culture. The time taken to screw on the 9 bolts was greatly in excess of the time required for English children (Jimi children aged 10 mean 80.0 s, English children aged 10, 42.3 s). The test therefore is insensitive because of the inherent difficulty for children in a culture where nuts and bolts and the necessary screwing action are entirely outside their experience.

Measures of the total time taken or number of trials required to attain specified goals were made on the items in the motor impairment test. In some age-groups the numbers were too small for statistical analysis. The results are therefore presented in a simple fashion. In 5 of the 6 age-groups the children from the treated group performed better than the controls. In the one group (9 year olds) where this was not the case only 3 children from the treated group were available for testing. Overall the children from the treated group seemed to be at an advantage. These results are offered only in general support of the case that the treated group show better overall motor skills.

### Discussion

These two groups of ostensibly normal children differ significantly in their skilled motor ability. The difference is apparent when tasks requiring both speed and accuracy are examined, no difference exists on more gross measures of strength, or simple speed of movement. The findings are clear and significant, though much further investigation is desirable; for example, it would be valuable to examine practice effects as a measure of learning. The controlled trial of which this study forms a part provided a unique population of children in which to examine the consequences of dietary iodine deficiency, other variables being essentially the same for both treated and control groups. The evidence indicates that children whose mothers have a severe dietary iodine deficiency are at risk not only of endemic cretinism but of sub-clinical deficits which put them at a developmental disadvantage. As soon as it became evident that iodine was an effective prophylactic for endemic cretinism iodised oil was administered to women in the control group.

Malnutrition has neurological and psychological consequences.<sup>9,10</sup> The methodological and analytical problems associated with relating nutritional status to brain growth and mental development are formidable.<sup>11</sup> These difficulties are exacerbated when the deficits are less than severe because the problems of linking them with suboptimal psychological development are correspondingly greater and relations are difficult to tease out. Chronic and severe protein malnutrition during the prenatal and immediate postnatal periods when the mammalian brain is known to be growing rapidly have been associated with anomalies in brain growth and behavioural development in animals and man.<sup>12-15</sup> There is evidence also of such deficiency resulting in retarded or delayed motor development.<sup>16,17</sup>

The pathogenetic effect of iodine deficiency, whether acting by itself or through the thyroid, on brain differentiation and development is not fully understood. The difficulties of conducting field studies in developing

countries are greater than those in industrial countries; language barriers, cultural differences, lack of accurate information on age, imperfect understanding about the significance of events &c.<sup>18</sup> Although not absent, the extent of these confounding factors is less in this study because of the controlled nature of the trial and because of the relative cultural and nutritional homogeneity of the two cohorts of children. Evidence which lends support to our findings, though on smaller samples and with less control over other variables, has been reported.<sup>19,20</sup> Both these investigations report deficits in motor competence in children born to mothers on an iodine-deficient diet and thus further support the thesis that the consequence of iodine deficiency is not an all-or-none effect of endemic cretinism but rather gives rise to a range of deficits which may in turn lead to developmental disadvantage.

Endemic cretinism is now a disease of the third world only. Whilst its prevention is a laudable and feasible goal the likelihood that the motor and possibly mental performance of whole populations may be increased by iodine supplementation is of great medical and social importance. The evidence presented here indicates that iodine deficiency may significantly affect general neurological development in the fetal period. Whilst iodine deficiency is not as widespread as protein malnutrition it is more easily remedied.<sup>21</sup>

We thank Miss D. Alberman, Mrs S. Moss, Mrs J. Hartshorne, and the staff of the Anglican Mission at Koinambe for their assistance. We also thank the staff of the Papua New Guinea Departments of Public Health and Education for permission to conduct the study and for their support and assistance. The investigation reported was made possible by a grant from the Wellcome Trust.

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## CHLOROQUINE-RESISTANT PLASMODIUM FALCIPARUM FROM EAST AFRICA:

### Cultivation and Drug Sensitivity of the Tanzanian I/CDC Strain from an American Tourist

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**Summary** A strain of *Plasmodium falciparum*, designated Tanzanian I/CDC, from an American tourist returning from Tanzania, was isolated in vitro and in the *Aotus* monkey. Clinically, the infection showed a late recrudescence pattern of chloroquine resistance. In 2 inoculated *Aotus* monkeys, the infection recrudescence after a dose of chloroquine (40 mg/kg) curative for sensitive *P. falciparum* strains in the *Aotus* monkey. In 4 additional monkeys two primary infections and one of the recrudescence parasitaemias were cured with a 100 mg/kg dose of chloroquine; the second recrudescence parasitaemia was cured with an additional 40 mg/kg dose of chloroquine. The 48 h in-vitro chloroquine-sensitivity test demonstrated that the Tanzanian I/CDC strain had a pattern of chloroquine resistance similar to a reference resistant strain, the Vietnam-Oak Knoll (FVO). These studies reinforce reports which suggest that chloroquine-resistant malaria is being transmitted in East Africa.

### Introduction

RESISTANCE to chloroquine in *Plasmodium falciparum* was first recognised in 1961 by Moore and Lanier<sup>1</sup> in 2 malaria cases from Colombia, and has since been detected in South America, Panama, Southeast Asia, Oceania, and the Indian subcontinent.<sup>2</sup> The drug prophylaxis and therapy of chloroquine-resistant *P. falciparum* has become a major public health problem.

Until recently, in sub-Saharan Africa, the area of the world with the most intense *P. falciparum* transmission, isolated reports of *P. falciparum* resistant to chloroquine have remained open to challenge, on the basis of World Health Organisation (W.H.O.) criteria, of the adequacy of chloroquine therapy or supervision of patient follow-up.<sup>2</sup> In a 1966 report, Jeffery and Gibson<sup>3</sup> were unable to confirm earlier reports of chloroquine resistance from Upper Volta and Liberia. Bruce-Chwatt<sup>4</sup> was unable to find convincing evidence of resistance to chloroquine in Africa up to 1970. Since then, however, additional reports from Africa<sup>5-7</sup> have raised the strong but uncon-

### DR CONNOLLY AND OTHERS: REFERENCES—continued

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