Commentary: From iodine deficiency to anomalous fetal development

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It was fortuitous that I was the District Medical Officer (DMO) for the Western highlands district of Papua New Guinea (PNG) in 1966. At that time, McCullagh had already carried out pioneering work using intramuscular iodinated oil as a depot preparation for treating the goitre of iodine deficiency and had given a clinical description of the associated endemic cretinism found in that area. It was Basil Hetzel’s perspicacity that recognized the importance of the problem, not only for goitre but also for endemic cretinism.

It was a serendipitous observation that goitre and cretinism had been reported from the Jimi Valley of the Western highlands district of PNG. The Jimi Valley was a remote area, access to which was made by the first administrative patrol in July 1953 followed by the establishment of an administration patrol post in 1958. As late as 1966, there was no vehicular access to the valley but four small airstrips enabled access and catered for provision of supplies and dealing with emergencies. This background of remoteness with difficulty of access provided an ideal milieu for a controlled trial.

The role of dietary iodine deficiency in the genesis of endemic goitre had been recognized for over a century. The geographical co-existence of goitre with endemic cretinism had also been noted over many years. Paracelsus in 1587 reported, ‘but to speak of these creatures that they perchance also have defects of the body, that is they carry growths with them such as goitres and the like: this perhaps is not a characteristic of fools, but also of others, however it fits most of them’. However, although in some areas the introduction of salt iodization had been accompanied by a decline in the prevalence of endemic cretinism; in other areas, a decline in the prevalence had been noted before even the recognition that iodine had a pivotal role in the development of endemic goitre. Endemic cretinism declined in prevalence in parallel with economic and social development. It was this situation that led to the decision for a controlled trial being the only route to providing a definitive answer to the problem. It was agreed that Ian Buttfield would perform the initial patrol giving the intramuscular iodine and placebo injections.

Meeting at my house in Mount Hagen early in 1966, Basil Hetzel, Ian Buttfield and I discussed the mechanics of carrying out the trial. In view of the remoteness of the area and the scattered population involved, this phase was no sinecure. Nevertheless, Ian and his newly wed wife deserve unreserved congratulations for their achievement for enrolling a trial population of 16,500. It was the intention that Ian would follow up the trial, however, subsequent events conspired against this. Three years later, in 1969, there had been no follow-up by which time I had completed my stint of DMO for the Western highlands and had been made DMO for the Sepik district stationed in Wewak. Concern at the failure to follow up led to my seeking and being granted permission by the Director of Public Health Department, Roy Scragg, to carry out a follow-up patrol. The initial follow-up patrol was successful in examining 60% of the children born to the trial population. My self-congratulation in achieving this level of success was short-lived. On telephoning Roy Scragg, he gave orders for me to return to the Jimi Valley and examine the missing 40%. After a short rest, a second follow-up patrol was carried out that increased the success rate to 90%. Again, a call to Roy Scragg merely elicited the response to return to catch the remaining 10%. My chagrin at yet another period of absence from home and family was considerable. Nevertheless, after the third patrol, 98% of the infants born into the trial had been examined. This was my introduction to epidemiological research. Roy Scragg had impressed on me the importance of reducing the non-response rate in epidemiological studies. This proved a life-changing event. On telephoning Roy Scragg, he gave orders for me to return to the Jimi Valley and examine the missing 40%. After a short rest, a second follow-up patrol was carried out that increased the success rate to 90%. Again, a call to Roy Scragg merely elicited the response to return to catch the remaining 10%. My chagrin at yet another period of absence from home and family was considerable. Nevertheless, after the third patrol, 98% of the infants born into the trial had been examined. This was my introduction to epidemiological research. Roy Scragg had impressed on me the importance of reducing the non-response rate in epidemiological studies. This proved a life-changing event. It led from having the administrative responsibilities of a DMO to a position in the Institute of Medical Research in Goroka with the remit of the continued follow-up of the trial and an assessment of the problems of iodine deficiency in other areas of PNG.

The main objective of the trial was achieved by demonstrating that the relief of iodine deficiency in...
women was able to prevent endemic cretinism. An important observation was that prevention was possible only if the iodine was provided before conception.2 The observation that the cerebral impairment of endemic cretinism occurred prenatally had been implied previously, although formal supporting evidence had not been available.

Subsequent follow-up of the trial population using a variety of tests to assess psychological and motor performance revealed subclinical deficits that placed the children, whose mothers were in the control arm of the trial, at developmental disadvantage.7,8 Furthermore, levels of cognitive and motor performance in the children correlated with the maternal thyroid hormone levels during the pregnancy.9,10 Thus, the overt clinical abnormalities of endemic cretinism were complemented by a shift of the overall frequency distribution of motor and intellectual performance to the poorer end of the scale.

The trial was not the end of the story in the Jimi Valley. Repeated observations, not only of those children born into the trial but including many born before the introduction of iodine prophylaxis, showed that there had been a rapid rise in the prevalence of cretinism that post-dated the first contact with Europeans in 1953. Prior to European contact, the local currency was salt, the production of which entailed a journey of 2–3 days and 1–2 months of careful evaporation of saline found in volcanic pools. Early European contacts, appreciating that salt was the local currency, imported salt (non-iodized) for the purchase of provisions. This source of salt became so easily available for the inhabitants of the Jimi Valley that they ceased producing salt from the volcanic pools. It so transpired that the volcanic salt was highly iodized.11 Thus, not only was the administration of iodine able to prevent endemic cretinism, but also the withdrawal of a rich source of dietary iodine precipitated an epidemic of the disease. To place the magnitude of the problem in the Jimi Valley into context, among infants born in 1965, one in seven was an endemic cretin.

It frequently occurs that one area of research generates other ideas that need investigation. Endemic cretinism is a form a cerebral palsy (CP) presenting with di-/quadriplegia and mental disability as the presenting features. Only deaf-mutism that is an important feature of endemic cretinism is unusual in clinical descriptions of CP. The cerebral impairment that presents as CP occurs pre-partum in the majority of cases with only ~20–25% being intrapartum or early neonatal.12,13 Having this in mind, I started a population-based register of CP for Merseyside, anticipating that some other dietary factor or teratogen would emerge as a causative factor. Whereas this line of approach was unproductive, a more fruitful line of research emerged. The register confirmed the frequently reported increased risk of CP among monochorionic, monozygotic, multiple gestations. A national survey of twin gestations in which one conceptus was a stillbirth revealed a very high prevalence of CP (1 in 10) or other cerebral impairment (an additional 1 in 10) in the surviving co-twin.14 The imprecision in recording of early fetal deaths in multiple gestations15 led to the hypothesis that many cases of CP in apparent singletons was attributable to the ‘vanishing’ twin.16 A proposed pathogenic mechanism is that feto-fetal transfusion leads to demise of one conceptus and cerebral impairment in the co-conceptus.

This concept needs to be explored further. Children with CP are at significantly increased risk of a variety of congenital anomalies compared with the general population of children.17,18 A unifying hypothesis is that both the CP and the coexistent other congenital anomalies have the same pathogenic mechanism, namely episodes of feto-fetal transfusion imbalance.19 If the brain impairment presenting clinically as CP may be explained by feto-fetal transfusion, why should this be any different from linking the genesis of congenital anomalies affecting all other organ systems to the same pathogenic mechanism? The timing of the feto-fetal transfusion will be critical, depending on the stage of organ development. For example, cardiac development is complete by week 9 and anomalous cardiac development may occur only if development is affected prior to completion. Furthermore, if development is affected at such an early stage of gestation, it is inherently more likely that co-conceptus development is also compromised sufficiently severely to cause its early demise. Thereby, the fetus with the cardiac anomaly will be born a singleton.

The development of this hypothesis has stemmed from the iodine deficiency story. The hypothesis of feto-fetal transfusion, if subsequently proven, has enormous potential for the prevention of CP and congenital anomalies affecting other organ systems. As with iodine deficiency, this has worldwide implications for the global prevention of a major cause of fetal and infant death and disability.

Conflict of interest: None declared.

References

Commentary: From iodine deficiency in Papua New Guinea to a global programme of prevention

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Our research work in New Guinea [at this time, I was Professor and Head of the University of Adelaide, Department of Medicine at the Queen Elizabeth Hospital (QEH), Woodville SA.] carried out in collaboration with the Papua New Guinea (PNG) Public Health Department of what was then a Territory under Australian colonial administration, eventually led to a global UN programme for the elimination of brain damage due to iodine deficiency.

It began in 1963, when I was asked by the Editor of the Medical Journal of Australia to review a paper by Dr Terry McCullagh on the use of injections of iodized oil (Lipiodol®) in PNG.1 This was a new technology proposed to assist the control of the severe goitre problem in remote villages in the Highlands where iodized salt (the usual technology) could not be easily introduced. An initial controlled trial carried out by McCullagh, at the request of the then Director of Public Health Department (PHD), Dr John Gunther, showed that one injection of iodized oil would prevent goitre for up to 3 years.1 No laboratory work had been done to determine whether iodine deficiency was present nor just how effective the injection was in correcting the deficiency.

I visited PNG (Huon Peninsula) in October 1964 as a consultant to the PHD. I was impressed with the...