

## Duncan memorial lecture: part 1

### Dr Duncan's legacy in a remote New Guinea valley

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Dean, colleagues, I am very honoured by your invitation to give the Duncan lecture for 1997.

In speaking of Dr Duncan's legacy in a remote New Guinea valley, I would like to focus on the contribution made by research in cerebral palsy that has been carried out in Papua New Guinea and in Liverpool, dividing Duncan's legacy into three time periods: Past—up to 1979; Present—1979 to 1997 and Future.

#### The past, pre-1979: The Jimi Valley, endemic goitre and cretinism

The Jimi valley is a remote area in the mountainous Western Highlands Province of Papua New Guinea with a population of about 24 000 comprising four language groups. In the early days of the research access to the valley was by light aircraft, there were no roads and all travelling in the valley was on foot. Numerous flimsy bridges made of bamboo and suspended over the river by vines had to be crossed (fig 1).

Endemic goitre attributable to iodine deficiency, a worldwide public health problem, was common in many parts of Papua New Guinea.

In the person with severe iodine deficiency, the thyroid can be very large indeed, the size of a football. It is particularly prevalent in women of childbearing age because their iodine requirements are greater than any other population group. Goitre is least prevalent in adult men.

That iodine deficiency is the main cause of endemic goitre has been appreciated for over a century.<sup>1</sup> In areas where goitre is endemic, the disease of endemic cretinism also is sometimes found. In contrast with what is written in most paediatric textbooks, the endemic variety of cretinism is a syndrome of neurological impairment comprising mental retardation, spastic diplegia/quadruplegia, deaf-mutism and occasionally, strabismus. In most countries where the disease is prevalent, clinical hypothyroidism is not a feature of the syndrome. There are two varieties of cretinism. The sporadic variety, which is congenital hypothyroidism, is well described in textbooks and may be found anywhere in the world with a birth prevalence of about 1:3500.<sup>2</sup>

Endemic cretinism is a variety of cerebral palsy usually accompanied by deaf-mutism, mental disability and strabismus. Because endemic goitre is attributable to iodine deficiency and endemic cretinism is found only in areas where there is endemic goitre, it was hypothesised that endemic cretinism was also attributable to iodine deficiency. However, there is conflicting evidence concerning the hypothesis whether or not iodine deficiency was the cause of both endemic cretinism and endemic goitre. For this reason we decided to undertake a controlled trial using intramuscular iodinated oil for the intervention group and physiological saline for the control group. The



Figure 1 Suspension bridge over the Jimi river.

Table 1 Cretinism prevalence rates in the trial intervention and control groups

	Mothers injected before conception		Mothers injected after conception	
	Iodinated oil	Saline	Iodinated oil	Saline
Number of births	593	597	95	90
Number of cretins	1	26	5	5
Prevalence of cretinism per 1000 births	1.7	43.5	52.6	55.6

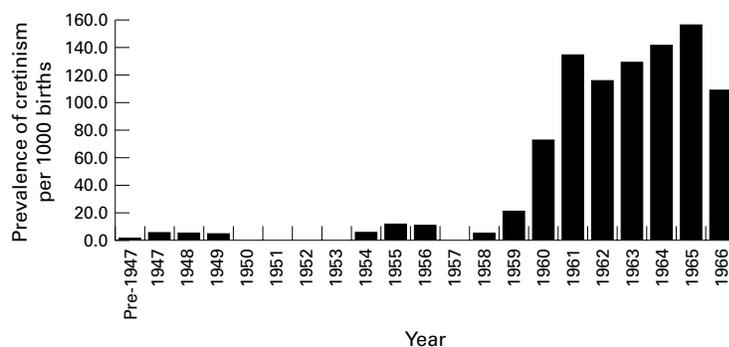


Figure 2 Trends in prevalence in cretinism.

story behind the use of iodinated oil given intramuscularly is, itself, of interest. The then Director of Public Health in Papua New Guinea, suffered from bronchiectasis and underwent radiographic bronchography with iodinated oil as the contrast medium. Several months later, a plain radiograph revealed droplets of the oil still present in the lungs. The director considered that, if the oil in his lungs was without untoward effect, it ought to be safe as a depot long term supply of iodine. Shortly afterwards he organised a trial of intramuscular iodinated oil for relieving and preventing endemic goitre that proved highly successful, many goitres vanished!<sup>3</sup>

The trial using a single intramuscular injection of iodinated oil to determine if it was effective in the prevention of neurological endemic cretinism started in 1966 and was carried out in the Jimi valley in the Western Nighlands of Papua New Guinea. Approximately 8000 people each in the intervention and control groups were entered into the trial. To obtain completeness of population coverage, the trial was conducted in association with a planned census of the population. This not only gave good population coverage but also provided copies of the name, sex, age and village of each person, which enabled the subsequent tracing of the women when they married into other tribal groups.

Subsequently I visited the Jimi valley on several occasions recording all pregnancies, and all births and examining the children born into the trial. I examined the children specifically for motor delay to diagnose the cerebral palsy, evidence of deaf-mutism and the presence of strabismus. Diagnosing mental disability was fraught with difficulty in this situation and I did not attempt to quantify it, however, the people themselves referred to the affected children as "long-long", which can be roughly translated from Pidgin English as being mentally retarded. By 1971, analysis of the data was show-

ing a clear result (table 1). Two conclusions can be drawn from table 1:

- (1) iodinated oil is highly effective in preventing the neurological impairment of endemic cretinism provided it is given before conception;
- (2) iodinated oil given after conception is ineffective, from which it can be inferred that the neurological impairment attributable to maternal iodine deficiency occurs during fetal development.

In the course of several visits to the valley, I was able to examine many "cretins" as they were brought to me because the people were aware of my interest in them. In all, there were 152 cretins for whom I had records. It was very striking that all were children except four who were adults. This is illustrated in a histogram that shows the annual prevalence of endemic cretinism per 1000 births (fig 2)

For a long time I assumed that the lack of adult cretins arose because affected children did not survive to adulthood. However, this could not be the whole answer because, in other equally primitive parts of New Guinea and in other equally under-developed nations, cretins survive well into adulthood. If the lack of adult cretins was not attributable to differential survival, what could account for the observed age specific pattern of the disability? Questioning the local populace always elicited the same answer, the disease came after the arrival of the white man! This fitted with the age specific pattern because the very first contact with the white man was in July 1953. The first missionaries entered the valley in 1957 and not long later they began the early infant welfare clinics. I wondered if these early clinics were allowing the cretins to survive but, as mentioned earlier, this differential survival could not be the sole explanation.

Alternatively, the possibility that cretins were deliberately killed soon after birth was considered but, following missionary influence and the imposition of a judicial system that forbade infanticide (and murder), the cretins were no longer disposed of in this way! This also could not be the explanation because the mothers denied practising the infanticide of cretins although they were quite ready to admit that they practised infanticide for multiple births. Furthermore, the mothers lavish considerable care on the cretins, carrying them to and from the gardens in that difficult terrain. It is pertinent that many of these cretins never achieve the ability to walk or do so only when they are several years old. A degree of neglect may set in when the mother has her next infant but this is a neglect arising out of necessity, the mother is physically unable to carry the new baby, a 3 or 4 year old cretin and all the garden produce for the evening family meal. When a new infant is born, the preceding child always gets left behind in the house when the mother leaves to work in the gardens each morning. A normal 3 or 4 year old is resourceful and certainly forages for him/herself and will catch, cook and eat anything that moves. The young children taught me how to light a fire without matches for cooking grasshoppers, praying

mantis, beetles and even very large spiders for culinary purposes! A cretin child, mentally and physically disabled, is unable to supplement the family evening meal with these exotic delicacies.

A third, and rather fanciful, possibility that occurred to me to account for the apparent recent epidemic of cretinism was that of cannibalism. Along the same lines that the disease Kuru was transmitted by the consumption of partly cooked human brain, I wondered if, before initial contact with the white man, ritual cannibalism involved the consumption of human thyroid glands! However, the people in the valley strongly denied that they ever practised cannibalism and I saw no reason to doubt their veracity.

At this juncture the sudden apparent increase in the prevalence of cretinism in the Jimi Valley was still an enigma. In discussion with Richard Hornabrook, who had carried out pioneer work on the epidemiology of Kuru, the question was raised concerning the source of salt that used to be consumed by the people in the valley. When this question was posed to the



Figure 3 Saline pools in the Simbai valley.

people themselves it evinced considerable excitement because, before the white man came to the valley, the salt making process was a significant social event involving the whole community. To understand the nature of the event, the local culture must be considered. Every tribal group in the valley had its own, strictly enforced, tribal land boundaries and trespassing of any tribe member beyond its boundaries was a recipe for tribal warfare. However, there would be observed at certain times, what the anthropologists in the area described as a *pax salina*. During this “salt treaty” the tribes from the Jimi valley would be allowed to travel unmolested through neighbouring territories to visit some salt pools. It meant a journey that crossed the Bismark-Schrader mountain range, the Simbai river and into the territory on the far side of the Simbai river. I travelled the route to visit the salt pools, it entailed two days of strenuous walking.

The salt pools, of which there were four within about a half hour walk of each other, were shallow and about six feet in diameter (fig 3). The area was volcanic there being a strong odour of rotten eggs in the vicinity, presumably because of hydrogen sulphide gas. The salt manufacturing process involved the erection of a pyramid of large stones over a fire. At the apex of the pyramid was a large flat stone over which a container was made of banana leaves surrounded by clay. Into this container water from the pool would be decanted and slowly evaporated, eventually producing a large disc of salt. The journey and the salt manufacture was a major communal event, the people would camp by the pools for one or two “moons” making sufficient salt, not only for their own use, but also for trading purposes. Anthropologists describe the salt trade routes as extending along the Simbai valley, across the Bismark-Schrader range and along the Jimi valley, across the Waghi-Sepik mountain range and along the Waghi valley. Salt was their currency with which they purchased brides, pigs, axes and other goods. It is pertinent that the English word “salary” comes from salt because salt was the currency here many centuries ago.

When the first patrol officers, gold prospectors and missionaries came to the valley, they were aware that salt was the currency and brought salt into the valley for trading. This white man’s salt became so easily available that the local population considered it no longer worthwhile to undertake the arduous journey and weeks of salt manufacture by the traditional method. Descriptions by anthropologists state that the last salt oven closed in 1958. This fits so nicely with the epidemiological data.

To complete the causal inference that iodine deficiency led to the rise in prevalence of cretinism, it was necessary to show that the salt was high in its iodine content. I collected samples of water from two pools, the local names for which were Tumbi and Sangen and was also fortunate in obtaining some salt from one of the villagers who lived in the vicinity of the pools. Although the last salt oven had long ceased to exist, those people who lived near the

Table 2 Analysis of samples from saline pools in the Simbai valley

Spring water sample	Total salt (parts per million)	Iodine (parts per million)	Iodine:salt ratio
Tumbi	15 800	4.4	1:3590
Sangen	19 500	6.0	1:3250
Deionised water (control sample)	99	Not detected	—
Sample of salt contained iodine 189.1 µg/g; iodine:salt ratio 1:5300			

pools would collect the salt water in a large bamboo container and, after allowing it to evaporate in the sun, would have a small quantity of the salt for domestic consumption. The next problem was to get the water samples and the salt analysed for their iodine content. Laboratories in New Guinea and Australia were unable to help. I was due to attend a meeting in the USA at which John Stanbury, internationally recognised for his work on the thyroid and iodine, was to be present. At this meeting I gave him the samples with the instruction that he had to find iodine in them otherwise my hypothesis would be refuted! Hardly a scientific way to approach the testing of the hypothesis. Not long afterwards I was informed that the samples all had a very high iodine content (table 2).

The salt has about twice the amount of iodine as the most heavily iodised salt produced commercially.

Thus it was shown that the administration of iodine to a community was highly effective in preventing endemic cretinism provided it was given before conception. Also, the withdrawal of a rich source of dietary iodine led to a sharp rise in prevalence of cretinism with almost 15% of the children born in the valley in 1965 being affected.

These observations have led to public health action at national and international level. In Papua New Guinea, as a short-term measure, a team was formed to give iodinated oil injections to all areas in the country affected by goitre. Internationally, largely through the efforts of Basil Hetzel, the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) has been formed and iodine is one of the two micronutrients, vitamin A being the other, which is the subject of an action programme by the World Health Organisation.

#### The present 1979–1997. The pathophysiology of cerebral impairment in cretinism and cerebral palsy

For the present I refer to my years in the academic Department of Public Health here in Liverpool. The research has progressed in a number of areas.

The research was directed towards clarifying the effects of iodine deficiency. One question related to Rose's prevention paradox.<sup>4</sup> If iodine was effective in overcoming the overt clinical features in endemic cretinism, was it also effective in reducing possible sub-clinical deficits—that is, might the administration of iodine to an iodine deficient population raise the mean motor ability/intelligence of that population? If so, the potential public health value of iodine supplementation for a population would be considerably improved. To test this, Kevin

Connolly, Professor of Psychology at the University of Sheffield, and I collaborated to apply measures of motor and cognitive function to the children born into the trial.

It is appropriate to interpose an anecdote at this stage. On Kevin's initial visit to the valley, our first day of testing the children was to be at a village about 3–4 hours walk from the mission station where we were temporarily housed. Our intention was to walk to the village, carry out the psychomotor testing of the children and make the return journey the same day. An arduous day's work was anticipated, quite how arduous was not appreciated till much later. We reached the village, tired but with a sense of achievement and recuperated physically during the period of testing the children. The return journey to the mission station was proceeding uneventfully until Kevin stumbled and fell. He was obviously in considerable pain and his statement "I think I have broken something, I heard it crack" was extremely worrying. We were still some way from the mission station where we had left all our clothes, bedding and food. With great difficulty and by a combination of being carried and hopping, Kevin and I reached an area where there were some houses belonging to the local people. I removed Kevin's boot and sock to reveal a badly swollen ankle. He had sustained a Pott's fracture.

What to do next was a question that was exercising my mind when the local medicine man approached and enquired, in Pidgin English, if I wished him to treat the broken ankle. Kevin, who did not understand Pidgin English, wanted to know what was being discussed. I explained all to Kevin seeking his opinion as to the desirability of the medicine man practising his local therapeutic knowledge. Kevin's response was to pass the decision back to me saying "You are my doctor, what do you think should be done". In the interests of science I responded that I would dearly like to find out what the local treatment entailed! This exchange ended with us giving permission for the local medicine man to practise his therapeutic skills. He promptly disappeared into the bush and came back with some large leaves that he proceeded to stroke up and down the fractured ankle. The leaves turned out to be a variety of stinging nettle and its effect was evident by the urticaria that developed! The treatment was only an example of the counter irritation technique that was part of our therapeutic armamentarium in years gone by. The theory behind it is that, if someone is in pain, apply another source of irritation and the original pain will be ameliorated.

Kevin and I spent an uncomfortable night in a smoke filled chimney-less hut that is typical for the area, keeping the fire going all night because of the cold. The following morning a stretcher was constructed to carry Kevin back to the mission station. The mean height of the local people is about five feet so they built a small stretcher!

To Kevin's consternation insult was added to injury by his being strapped to the stretcher with vines having him in a fetal position rather like a trussed-up chicken! (fig 4). He had

visions of being part of some cannibalistic ritual! The reason for the precaution became apparent on the return journey. At one point the path becomes very narrow as it traverses the face of a landslide. In negotiating this, Kevin's four stretcher bearers had to get into single file. In doing so, the stretcher tipped sideways and Kevin looked straight down the mountainside. His characteristic response was "Peter, I think I would rather get out and walk!"

Returning to the main text, we carried out a series of motor and cognitive tasks. The results of these tests showed that there were significant differences between the intervention and control groups of children in the speed and accuracy of the motor tasks and in cognitive tests.

A second line of research concerned the mechanism by which severe maternal iodine deficiency affected the maturation of the fetal brain. Because the cerebral impairment occurs during early fetal development, an attempt was made to obtain blood samples from women in early pregnancy. It was not difficult recognising



Figure 4 Kevin being strapped to a stretcher.

pregnancy in the stage of late gestation, but doing so for early gestation was much more problematical. This was partly because the women were shy and reluctant to admit that they were pregnant but also, probably, because they do not date the pregnancy from the first day of the last menstrual period. Their habit of breast feeding for about three years makes the last menstrual date an unreliable indicator of pregnancy and they date a pregnancy probably from when fetal movements are first felt—that is, at 16–18 weeks after conception. In an attempt to overcome the difficulty of making a diagnosis of early pregnancy, blood samples were taken from as many women as possible whose last child had been born at least three years previously in the hope that some women may have recently conceived. These samples were assayed for thyroid hormone concentrations at the Middlesex Hospital in London, the difficulties entailed in separating and freezing the serum in the field and the transport of the frozen samples to London is another story.

The major serological abnormality found in those who are iodine deficient, is a reduction in serum thyroxine (T<sub>4</sub>). The serum tri-iodothyronine (T<sub>3</sub>) value level remains within normal limits so that a person who may be severely iodine deficient is, nevertheless, clinically euthyroid.

Subsequently, the children born to the women were psychometrically tested on several occasions. Consistently a correlation was observed between the mother's T<sub>4</sub> level during the pregnancy and the level of the child's motor and cognitive performance. There seems to be a continuum of damage dependent on the maternal T<sub>4</sub>. Fetal or neonatal death occurs with extremely low levels of maternal T<sub>4</sub>. At slightly higher levels of maternal T<sub>4</sub>, the children manifest clinically recognisable neurological abnormalities. At higher levels still of maternal T<sub>4</sub>, subclinical measures of psychomotor function correlate with the maternal T<sub>4</sub> measured when the child was in utero.

As a result of these observations, a hypothesis was proposed that unifies the differences between the cerebral palsy and deaf-mutism of endemic cretinism and the clinical syndrome of congenital hypothyroid cretinism.<sup>5</sup> The normal cellular functioning of most organs is dependent on circulating T<sub>3</sub>. Brain cells differ in that they are dependent on circulating T<sub>4</sub> and possess an intracellular deiodinating enzyme to convert T<sub>4</sub> to T<sub>3</sub>. Thus T<sub>4</sub> is crucial to normal cerebral function from conception to death. In early gestation, before the fetus can manufacture its own T<sub>4</sub>, it is dependent on the mother's T<sub>4</sub> and any deficiency at this stage of fetal neurological maturation leads to cerebral palsy, deaf-mutism and mental retardation. In late gestation and during infancy, the fetus/infant manufactures its own T<sub>4</sub> and a failure of this mechanism leads to the clinical picture of congenital hypothyroidism. Even in later life, myxoedema madness and other clinical neurological abnormalities testify to the dependence of the brain on normal thyroid function.

Because cretinism is a variety of cerebral palsy and because cerebral palsy is the

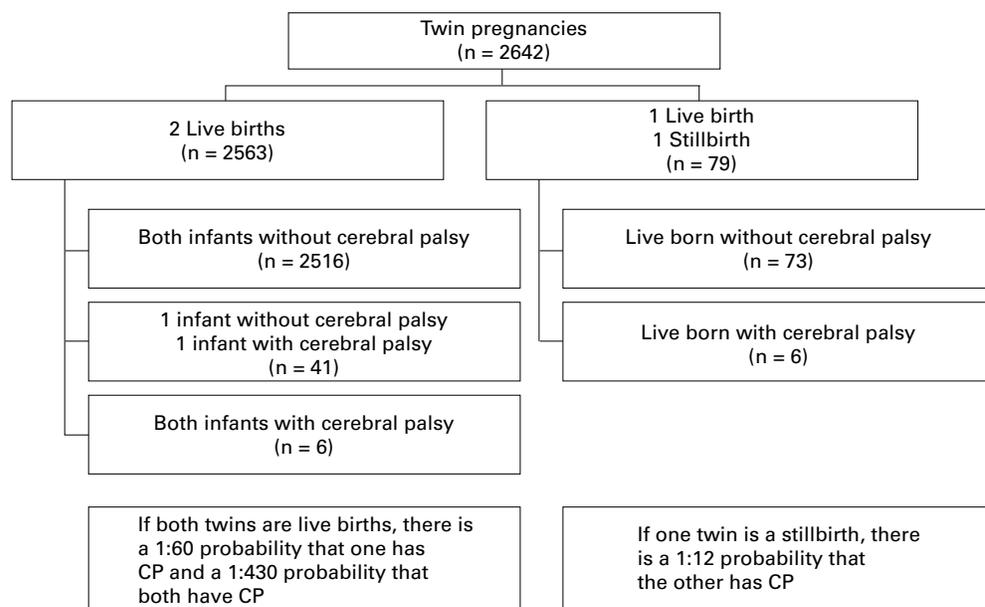


Figure 5 Cerebral palsy in twins in Mersey Region 1982–89.

commonest cause of severe physical disability among children in this country, in 1980 we started to maintain a register of cases of cerebral palsy in children in Merseyside and Cheshire. It has always been of concern that there is no routine data source that allows the monitoring of the prevalence of important childhood disabilities. In the case of cerebral palsy, such monitoring becomes particularly relevant because of the enormous technological improvements in neonatal intensive care. There have been dramatic improvements in the chances of survival of very small infants.

I remain indebted to Theresa Cooke for maintaining the register with such thoroughness for so many years. One of the main observations arising from an analysis of the register data is that the prevalence of cerebral palsy is increasing among low birthweight infants but is unchanged among infants weighing over 2500 g.

Among the birthweight groups, the increase in prevalence started progressively later the lower the birthweight group. The important question arising from these data is whether the increase in survival is attributable to better survival of prenatally damaged infants. If so, as obstetric and neonatal intensive care further improves, more cases of cerebral palsy will survive. Alternatively, in vulnerable extremely low birthweight infants, the cerebral palsy is caused by a failure to maintain normal blood pressure, respiration, etc. If this is so, improving neonatal care will lead to a decrease in cerebral palsy prevalence.

Another feature of interest arising from the cerebral palsy data concerned multiple births. Twins are at an increased risk of cerebral palsy compared to singletons. This risk is particularly high in the surviving twin if its co-twin is stillborn (fig 5).

To examine the effect of a stillbirth on its surviving co-twin, all cerebral palsy-stillbirth twin pairs were selected from the cerebral palsy register. We knew that if one of the pair had

been a stillbirth because it was recorded in the obstetric notes, usually as a fetus papyraceus. There were 18 such pairs on the register and the names of the survivors were given to the Office for National Statistics with the request to trace the birth registrations and determine how many of the stillbirths had been registered. Six of the 18 stillbirths had not been registered. In effect, the six survivors with cerebral palsy were considered to be singletons. This led to the query as to how many apparently singleton cases of cerebral palsy were associated with an unrecognised death of a co-twin in utero.

This brings me to the final part of my talk this evening.

#### The future: 1997- a hypothesis to test

It has been noted, in obstetric case reports, that one stillbirth in a monochorionic twin pregnancy has adverse prognostic significance for the surviving co-twin. Cerebral palsy, mental retardation and other disabilities have been reported as adverse outcomes for the surviving livebirth. The crucial feature in all these reports is that the twins are monochorionic, they share the same circulation. Monochorionic twins are a subgroup comprising about 70% of all monozygotic (identical) twins.

The use of ultrasound in early gestation has revealed that a significant proportion of women start with a multiple pregnancy but only a singleton infant is delivered. A phenomenon referred to by obstetricians as the “vanishing” twin. The vanishing twin, or an unrecorded stillbirth in a twin pregnancy may have a profound effect on the liveborn survivor. This led Richard Cooke and me to propose the hypothesis that spastic cerebral palsy in apparently singleton children is attributable to death of a monochorionic co-twin in utero.<sup>6</sup>

Fetal death of one twin may easily be missed. In such cases it may be misreported that there is infarction of the placenta. However, on dissecting the area of “infarction”, it can sometimes be shown to contain a fetus papyraceus.

The skeletal components of fetus papyraceus can also be shown clearly in a placental radiograph.

In our future research, therefore, it is proposed to test the hypothesis is several ways:

- (1) through the Office for National Statistics for England and Wales and the Scottish Information and Statistics Division for Scotland, for all registered twin pregnancies in which one of the twins was a stillbirth, to contact the general practitioners of the surviving child and determine if the child has a disability. This will enable a quantification of the proportion of all cerebral palsy that is attributable to the registered death of one fetus in a multiple pregnancy.
- (2) at the Liverpool Women's Hospital, to follow up all women who have twins diagnosed at routine ultrasound to determine how many of the twins "vanish" and if the survivors have a disability.
- (3) a case control study of children with cerebral palsy to determine if the vanishing twin is a risk factor.
- (4) in Bristol, as part of a large cohort study, 12 000 children are being followed up among whom are about 30–40 cases of cerebral palsy. The placentas of these pregnancies have been stored and it is proposed to carry out a detailed pathological examination of them to determine if a dead twin or its remnants are present.

A further piece of supportive evidence is to be found in an analysis of national birth and death registration data on twins of like and unlike sex. The Weinberg rule can be applied to these data to distinguish between mono- and di-zygous twins.

For England and Wales 1982–91, there were over 70 000 sets of twins. In mono- compared with di-zygous twins there is a relative risk of 1.8 ( $p < 0.0001$ ) that both will be stillbirths, of 1.8 ( $p < 0.001$ ) that one will be a stillbirth and, if one is a stillbirth, the relative risk of the liveborn survivor dying in the neonatal period is 2.3 ( $p < 0.001$ ).<sup>7</sup> I suggest that, in a

monozygotic twin pregnancy, the division process leads to a lethal anomaly in one fetus and that the demise of one fetus has a deleterious effect on its co-twin, which is manifest as a continuum of damage. At one extreme, the co-twin also dies in utero—that is, both are stillbirths. A less extreme outcome is that the co-twin is live born but has sustained cerebral damage that proves lethal in the neonatal period. The least severe outcome for the co-twin is a range of cerebral impairment that may manifest itself as cerebral palsy, severe learning disability and some non-cerebral impairments such as the gut atresias, renal agenesis (Potter's syndrome) and syringomyelia.

If the research is to become part of Dr Duncan's legacy, the hypothesis needs to be confirmed. Then the mechanism of cerebral damage can be pursued so that a strategy for prevention can be drawn up. Cerebral palsy and mental retardation are the commonest causes of severe disability in children and any preventive measures have important health, educational and social service implications.

The question, whether or not separation of identical twins after birth has a deleterious effect, is sometimes asked. I conclude this Duncan lecture by putting to you the hypothesis that death of one monochorionic twin before birth may have a profound and lasting effect on the co-twin.

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