Iodine, alcohol, and mental deficiency

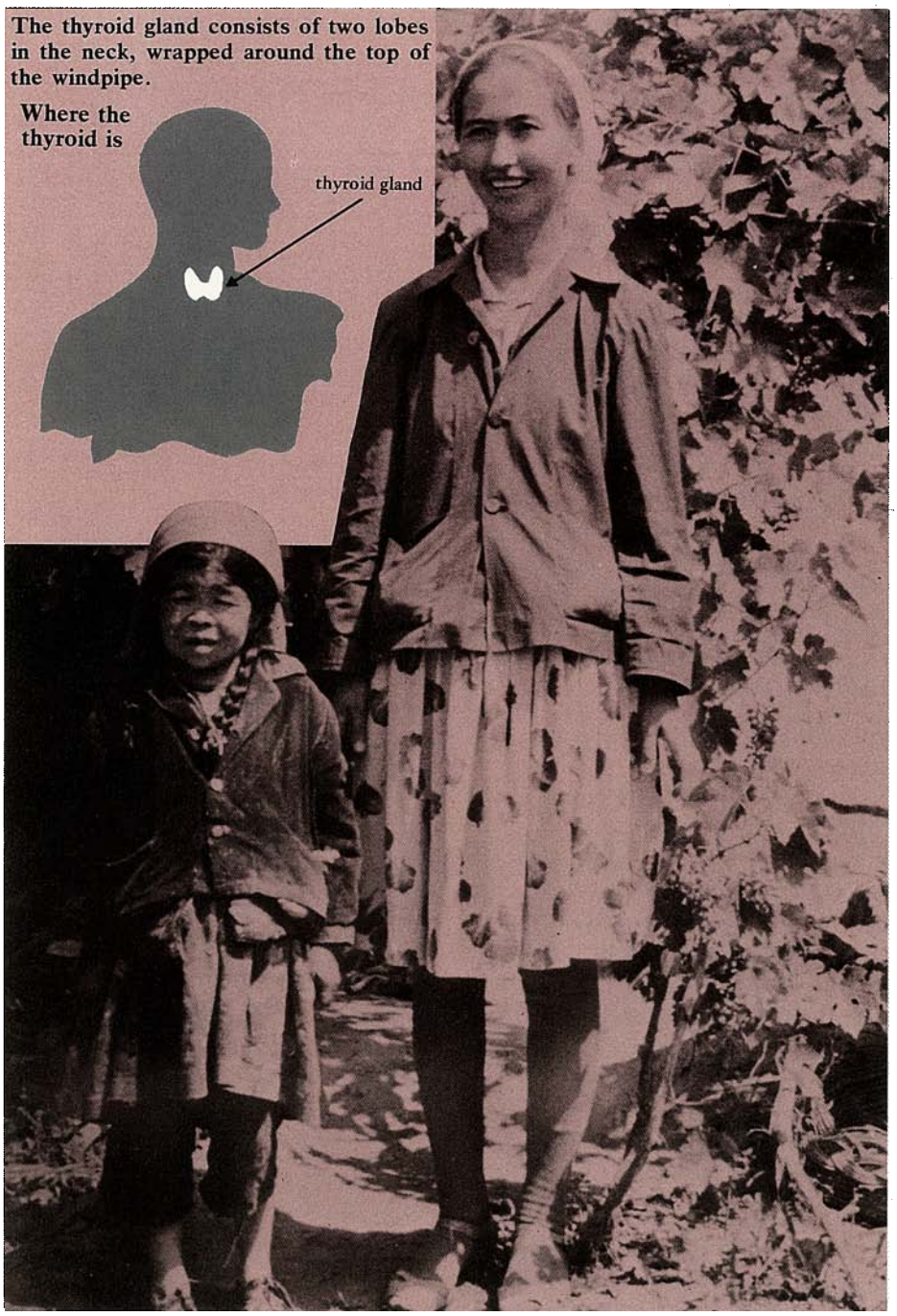
A child's surroundings play an important role in shaping the future adult — sociologists and psychologists have long agreed on that. But only in recent times have scientists been able to identify some serious dangers in the earliest environment of all: the womb.

Several of these dangers are of our own making. Mothers-to-be should nowadays be aware that smoking during pregnancy puts a baby at risk, and who can forget the thalidomide tragedy? Researchers in the CSIRO Division of Human Nutrition are investigating the pre-natal effects of alcohol (early experimental results, obtained with sheep, won headlines like 'Boozy ewes show perils of drinking') and also an environmental factor less easily controlled — a shortage of iodine in the diet.

We need the element iodine for the thyroid gland to make two hormones, known to physiologists as T_3 and T_4. As their full names, triiodothyronine and tetraiodothyronine, suggest, iodine enters into the composition of both hormones, with three atoms in a molecule of T_3 and four in T_4, which is also called thyroxine.

These thyroid hormones help to control the release of energy inside cells. If your diet lacks iodine and you cannot make them, one of your symptoms will be a poor ability to regulate your body temperature; you will need to switch on a heater far more readily than most people.

Some unfortunate individuals have been deprived of an adequate supply of iodine all their lives, simply because the local soil and water contain low levels of the element. These people display a wide variety of symptoms, the worst of them causing severe incapacitation.

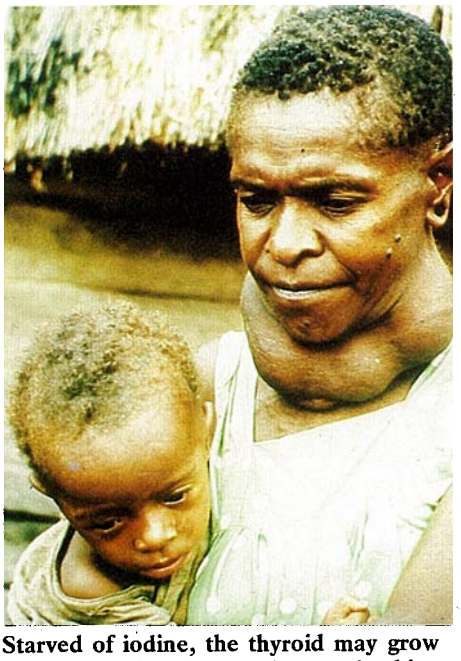


Two Chinese women in their mid twenties: a 'barefoot doctor' and a cretin. Characterized by stunted growth and mental deficiency, cretinism is particularly common in certain parts of the world.

Many sufferers have a goitre, a more or less massive swelling in the front of the neck brought about by excessive growth of the thyroid gland. Goitres have various causes, one being iodine deficiency, which results in a bizarre breakdown in the body's internal communications. In a human being the thyroid is stimulated to grow by a message, in the form of a hormone, from the pituitary gland just beneath the brain.

If the thyroid grows and functions normally, it eventually secretes its own hormones, T_3 and T_4, and when these reach a sufficient concentration in the bloodstream, the pituitary 'knows' that it is time to stop secreting its own messenger chemical, the thyroid-stimulating hormone. The subsequent growth and activity of the thyroid are nicely controlled by a balance of these chemical messages passing between the thyroid and the pituitary.

A shortage of iodine breaks this chain of command and counter-command. Without iodine the thyroid cannot synthesize T_3 and T_4, or at any rate not in sufficient quantities to provide the information 'feedback' (a team borrowed by physiologists from engineers) for which the pituitary is waiting. The pituitary therefore continues to produce its stimu-



Starved of iodine, the thyroid may grow unchecked, forming a goitre, as in this Papua New Guinean woman.

latory hormone, and the thyroid grows on, unchecked.

Cretins

But the pathology of iodine deficiency is much more complicated than that. Not only do some goitres have other causes, but some people, although short of iodine from the beginning of their lives, do not develop a goitre. However, they may suffer a number of other symptoms, including poor physical and mental growth. The bones may be slow to ossify; the skin may be dry and the tongue swollen; the nose and face may be broad and flat.

Many patients have poor physical coordination, and in extreme cases the brain's failure to develop fully leaves the patient a moron. Sufferers from all or most of these debilitating conditions have for centuries been called cretins.

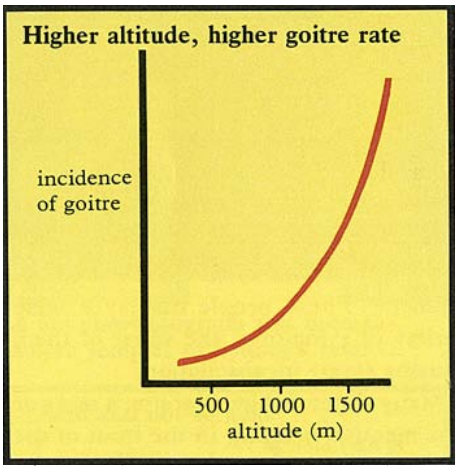
Certain geographical regions lack natural iodine — generally hilly or mountainous places well inland, where iodine has been lost through leaching or soil erosion and cannot be replaced by sea spray. A shortage of local iodine does not threaten the health of communities in modern developed countries, whose complex trade and marketing ensure that people eat foods from many different places. But in poor societies that depend on subsistence agriculture, iodine deficiency in the soil means deficiency in the diet, too.

The problem becomes particularly acute in small, remote communities such as mountain villages in Papua New Guinea, the Himalayas, and the Andes, whose inhabitants have little opportunity to obtain meat and grain from neighbouring communities, let alone seafood or the produce from distant iodine-rich farmlands.

Goitres and the various signs of cretinism occur especially frequently in particular geographical areas, and scientists therefore use the terms 'endemic goitre' and 'endemic cretinism'. Although the link between these diseases and iodine deficiency is not simple and was for a long time denied by some scientists, clear evidence has accumulated during this century that such a link exists, and that if only iodine can be supplied to people in the right way and at the right time these diseases can be prevented.

Australia, as it happens, is a lucky country: only Tasmania has had a severe goitre problem, which in 1949 affected 20% of girls and 6% of boys aged 12–14. Twenty years later, goitres had virtually disappeared from the State, following the distribution of iodide tablets to schools and child health centres and the addition of iodate to bread.

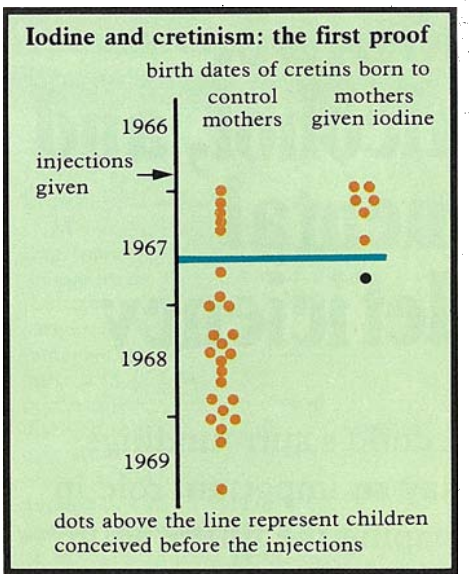
In many other developed countries goitres similarly declined, but scientists could not always attribute the improvement unequivocally to iodine. In Switzerland during the 1920s, for example, the frequency of goitres among military recruits declined from more than 50% to 14% without any iodization program.



In Papua New Guinea, Dr Buttfield and Dr Hetzel found far higher frequencies of endemic goitre in mountain villages than near sea level.

Subsequently the Swiss authorities introduced iodized salt, and by 1950 goitres were almost unknown among recruits. The district contributing the largest number of goitrous recruits was the only one that had not implemented the iodine program.

Results like these from various parts of the world suggested strongly that iodine helped prevent goitres, but they did not amount to proof positive — and such proof was essential before doctors could tackle the disease in countries where it remained a serious problem. In 1960 the World Health Organization estimated that at least 200 million people suffered from endemic goitre.



In 1966, many Papua New Guinean highland women received iodine injections: they bore no cretins after late 1967. The black dot represents a child of uncertain age; when Dr Buttfield and Dr Hetzel checked, they found it could have been born several months earlier (putting the dot above the line). This study and later trials elsewhere show that cretinism is prevented if mothers are given iodine before pregnancy.

Injections of iodine

About 20 years ago scientists obtained the proof. They gave injections of oil containing iodine to people living in regions of endemic goitre; the oil prevented goitres. A single injection proved sufficient to correct iodine deficiency for about 4 years.

However, the connection between goitre and cretinism remained obscure. Did cretinism result from iodine deficiency or from some other cause?

To find out, Dr Basil Hetzel, then Professor of Medicine at Adelaide University and now Chief of the CSIRO Division of Human Nutrition, and Dr Ian Buttfield of the Papua New Guinea Department of Public Health began in 1966 a controlled trial in the Jimi River district of the Western Highlands of Papua New Guinea — an area known for its high incidence of endemic cretinism. In each of the study villages, half the families received an injection of iodized oil; the other half (the controls) were given an iodine-free saline solution.

The results were striking. By early 1969 the control mothers had given birth to 304 children, of whom 21 showed signs of

neurological defects, including mental retardation. The mothers who had received iodine produced a similar number of children, 317, but only seven of these turned out to be cretins. Six of these seven were definitely conceived before the iodine injection, and the seventh may have been; doubt surrounded the child's age.

In the first 3 years of the trial 20 cretinous babies were definitely conceived after the injections, and all 20 were born to untreated mothers.

Clearly, then, a single injection of iodized oil given to a mother before pregnancy can prevent her child from becoming a cretin. This conclusion was subsequently confirmed by other researchers in Zaire and South America. Mass injection programs to prevent goitre and cretinism began in Papua New Guinea in 1971 and, later, in other countries, including Zaire, Indonesia, and China. As a result, cretinism has already disappeared both from Papua New Guinea and from central Java and Indonesia.

Sufferers from endemic cretinism do not normally have very low concentrations of the thyroid hormones in their blood, but their symptoms, which include mental deficiency, paralysis, deafness, and dumbness, suggest that the nervous system is not functioning satisfactorily.

The results of the controlled trials show that the permanent damage to a cretin is done during pregnancy; some process in the development of the embryo or foetus does not 'go according to plan'. Which process is it? And when is the damage done? If a woman has already been pregnant for a few months, will an injection of iodized oil do any good, or is it too late?

The sheep model

To find out the answers to these and related questions, in 1976 the Division of Human Nutrition began a series of experiments with sheep. The researchers chose this species for several reasons.

Salt is not always the best medium for distributing iodine: in desert regions the villagers make their own rock salt, and not everybody maintains an adequate iodine intake. Iodized-oil injections, given by 'barefoot doctors', are proving more successful.

Overseas work had already shown that the thyroid physiology of a ewe and her foetus quite closely resembled that of a human mother and her unborn baby. The sheep's large size makes it more amenable to investigation than is, say, a laboratory rat, and small mammals seem less prone than large ones to damage from iodine shortage.

Moreover, a lamb's brain, unlike that of many mammals, completes most of its development before birth. It also grows relatively slowly (gestation lasts 150 days) and its growth changes are therefore easier to detect than those in, say, a rat.

The researchers' first task was to create 'models' of women living in iodine-deficient regions, by depriving some ewes of iodine. It took Mr Brian Potter, who runs these experiments, and his colleagues 12 months to find a diet low enough in iodine. They eventually settled on crushed maize from a low-iodine district and pea pollard, which the Division makes into pellets.

The scientists add calcium and trace elements, and give the sheep deionized water to drink. On this diet ewes look alert and healthy, but their levels of thyroid hormones fall.

Housed in a shed at Glenthorne, a former sheep farm and now the Division's experimental station on the outskirts of Adelaide, the first ewes soon began to chew through the timber of their stalls, as if they could sense that the wood contained some element missing from their official diet (the wood does indeed contain iodine). The scientists had to put each sheep in a metal cage to separate it from the wood.

To be sure that the experimental diet was healthy in all respects except its iodine content, the scientists fed the same food to a second group of ewes, which in addition received a single injection of iodized oil. A third set of animals that grazed on Glenthorne's pasture provided a standard of comparison for both the experimental (iodine-deficient) ewes and the injected controls.

Iodine has reduced goitres in China

village or commune	goitre rate (%) at start of iodized-salt program	goitre rate (%) after iodized salt distributed
Limiao	62·1	10·9 after 12 years
Heba	31·5	5·2 after 2 years
Wuchihe	44·7	2·9 after 22 years
Baimao	42·0	2·4 after 15 years

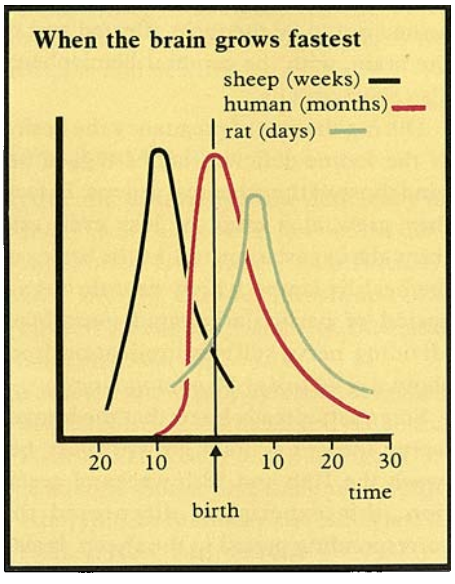
Lambs deprived of iodine throughout development show skeletal defects, such as these mis-shapen legs.

After about 7 months on their special diet, the ewes' T_3 and T_4 levels had fallen very low and, thanks to the feedback mechanism, the thyroid-stimulating hormone had reached a high concentration in the blood, causing visible goitres. At this stage all three groups of ewes mated with normal rams.

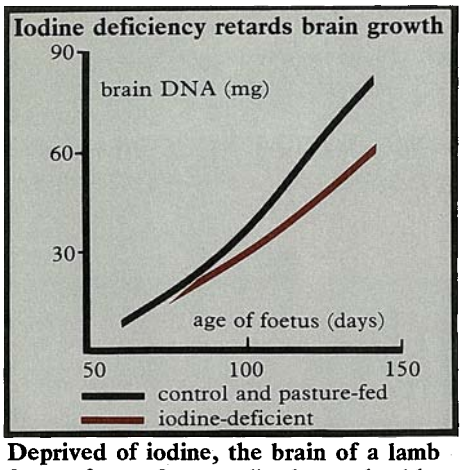
Poor brain growth

For the first 2 months, pregnancy seemed to proceed normally, but by the 70th day of gestation the experimental lambs had clearly fallen behind in their brain growth. Meanwhile the control lambs kept up with the pasture-fed group, showing that the inferior development of the experimental lambs must be attributed to lack of iodine.

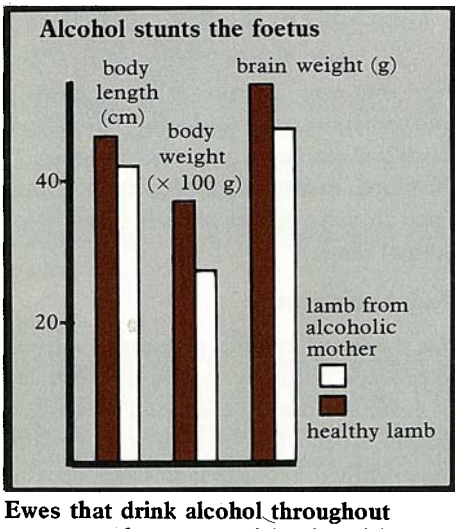
The CSIRO researchers carried out analyses of the brains' DNA content (a measure of the number of cells) and protein (to determine the average size of the cells) and found that the iodine-deficient



Sheep make good 'models' because the brain completes most of its development before birth. The human brain grows fastest at about birth, and the rat's after birth.



Deprived of iodine, the brain of a lamb foetus forms fewer cells than a healthy brain.



Ewes that drink alcohol throughout pregnancy bear stunted lambs with retarded brains.

lambs were simply not making as many brain cells as healthy animals. Dr Brian Cragg of Monash University confirmed this after examining sections of the experimental brains with both light and electron microscopes. The cerebellum turned out to be the most affected part of the brain, with the cerebral hemispheres also short of cells.

During the rest of pregnancy the brains of the iodine-deficient lambs lagged behind those of the other two groups. In fact, they grew at a more or less even rate throughout gestation, unlike the brains of the healthy lambs, which went through a period of particularly rapid neuroblast (dividing nerve cell) multiplication from about day 40 to day 80 of pregnancy.

Scientists already knew that the human foetus showed a 'brain growth spurt' between the 10th and 18th weeks of gestation; this experiment discovered the corresponding period in the sheep. It also provided the first experimental demonstration in any species that iodine deficiency could cause defective brain growth.

At birth, the control lambs were normal, but the ones that had been starved of iodine had little or no wool, the epiphyses of their joints had not properly formed, and their heads looked curiously misshapen, with domed skulls and undershot jaws. They had enlarged thyroids but low levels of thyroid hormones from day 70 of gestation onwards.

While this experiment proved that iodine was essential for normal brain development, it left open the question whether iodine influenced the brain directly or via some other organ, particularly the thyroid. Mr Potter and Dr Graeme McIntosh, also of the Division, investigated the role of the foetal thyroid by removing it, between days 50 and 60 of gestation, from animals whose mothers had received a normal diet including iodine. When these lambs were born they showed much the same symptoms as the iodine-starved lambs, but less severely.

This experiment suggested that the thyroid could be playing a role in brain development. If so, how does the brain develop in the early weeks of pregnancy, before the foetal thyroid starts to function? One possibility worth exploring was that the mother's thyroid hormones crossed the placenta into the foetal blood-stream, stimulating the early development of the lamb's brain.

To test this idea, the CSIRO team removed the thyroids from some ewes being fed a normal diet. After about 6 weeks, T_3 and T_4 had almost disappeared from the ewes' blood, and the animals were mated with normal rams.

Back on schedule

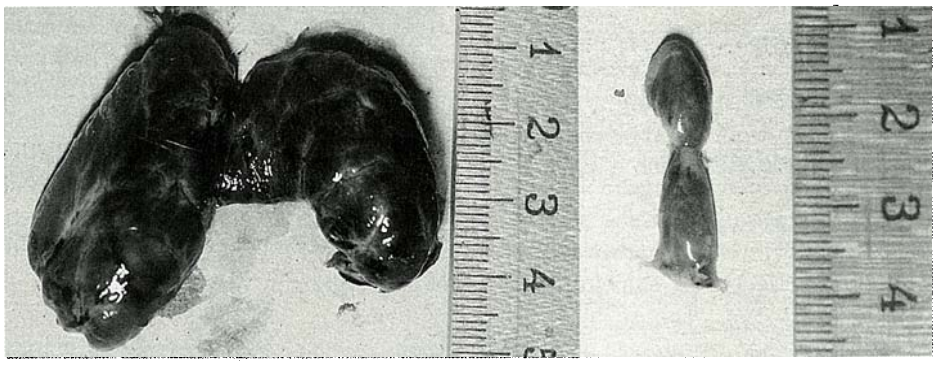
At first, the results mimicked those of the iodine-deficiency experiment: the experimental lambs' brains kept pace with the controls until the start of the growth spurt, when they lagged behind. But, intriguingly, by day 140 the experimental animals had caught up with the controls.

The researchers suggested that, when the growth spurt was due to begin, the experimental brain could not quite keep 'up to schedule' through lack of thyroid hormone, but once the foetal thyroid gland was fully functioning it brought the brain's development back on time, presumably by some feedback mechanism.

Furthermore, the lambs whose thyroids were removed during pregnancy — and whose mothers were fed a normal diet containing iodine — showed less severe symptoms than iodine-deficient lambs. Although unable to make their own thyroid hormones, the lambs could have received some hormone from their mothers across the placenta — a lifeline that could not be thrown from an iodine-starved ewe to her foetus.

Suggestive as all these experiments were, they did not conclusively establish that iodine's only role in brain development was as a component of thyroid hormones. Could iodine directly influence the brain itself?

The researchers gave foetal lambs a plentiful supply of iodine but deprived them of thyroid hormones. This they achieved by feeding ewes on a normal diet, removing their thyroids, and subsequently removing the foetal thyroids too, at about day 100 of pregnancy. This experiment produced even more severe effects than any of the previous ones. For the first time, the scientists could see the effect of totally excluding thyroid hormones from the foetus.

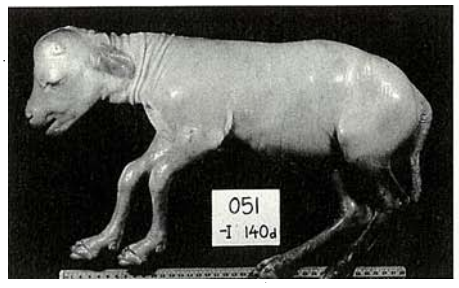


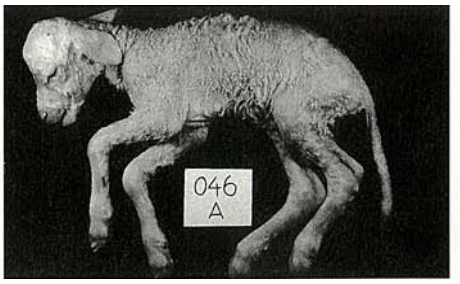
At birth, the thyroid of an iodine-deficient lamb (left) may be ten times the size of a healthy gland (right).

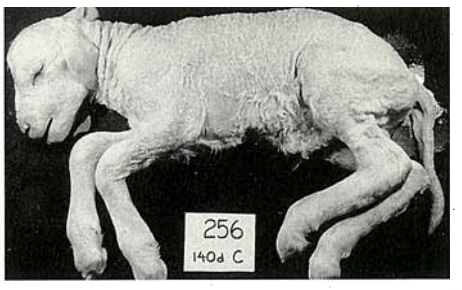
To put the issue of iodine's role beyond doubt, the scientists plan to remove the thyroids from both a ewe and her foetus, then give the ewe an injection of iodized oil at about day 100 of pregnancy. They do not expect to see any recovery in the brain's growth in the absence of thyroid hormones.

The scientists have also tackled the question of timing. How late in a woman's pregnancy is too late for an iodine injection to confer any protection against the risk of bearing a cretinous child?

To answer this question for the sheep model, the researchers injected iodine-deficient ewes with iodized oil two-thirds







Environmental effects on development compared: short of iodine (left), a newborn lamb forms a domed skull and lacks wool; alcohol (centre) may stunt body growth. Right: a healthy lamb.

of the way through pregnancy. The lambs showed remarkable powers of recovery: after the injection their brains, which until then had lagged in growth behind those of the controls, put on a spurt and by birth had almost caught up. However, the results of prophylaxis programs suggest that an injection at the equivalent stage of human pregnancy (the end of the second trimester — that is, after 6 months' gestation) would be too late to prevent severe damage to the baby's central nervous system.

Now the CSIRO scientists plan to repeat the sheep experiments with marmosets, which are small monkeys from South America, and much more closely related to humans. Perhaps marmosets will even more accurately model human brain development than sheep do, and help to resolve the 'how late is too late?' question.

International co-operation

In 1981 Dr Hetzel visited China as a member of a delegation from the Australian Academy of Science. While there, he was invited to visit Tianjin Medical College, where he met a group of scientists engaged in a research program set up in 1959 to combat endemic goitre and cretinism. China has an estimated two million cretins.

The Tianjin researchers had in recent years attempted to use laboratory mice as models of cretinism, but they had found it difficult to induce symptoms of iodine deficiency in these animals. Naturally, the Chinese scientists took great interest in the CSIRO sheep model, and last May the program leader, Professor Ma Tai, supported by the Australian Development Assistance Bureau, began a 3-month visit to the Division of Human Nutrition in Adelaide, to study the CSIRO team's procedures before himself setting up a sheep research program in Tianjin.

The Division's attraction for such a visiting scientist lies not only in the experimental model (the sheep) but also in the analytical procedures developed by Dr Gordon Jones and, since Dr Jones' retirement, Mr Bryan Belling for measuring very small amounts of iodine. These analyses play an essential role in monitoring, for example, the levels of iodine in the food given to the experimental sheep.

Chinese medical authorities are already tackling endemic goitre and cretinism with iodized oil, given either by injection (in which case, as Dr Hetzel and his colleagues found in Papua New Guinea, the effect lasts about 4 years) or orally (a less satisfactory technique, as the effect wears off in only half the time).

Parts of Indonesia also display high rates of endemic cretinism, and the Division of Human Nutrition has been collaborating with Diponegoro University in central Java in an assessment of the iodized-oil program that has been set up there. The Division has also contributed analyses of the iodine content of urine samples. These studies have confirmed that iodine injections prevent both cretinism and a more common co-ordination defect recognizable by the long time it takes a child to learn to walk.

In early 1982 Dr Mulya Utama of the Indonesian National Iodine Reference Laboratory spent 2 months in Adelaide to study the Division's methods of measuring very small amounts of iodine.

Alcohol in pregnancy

The Division has found the sheep a valuable model for another serious condition, the foetal alcohol syndrome. Epidemiologists have found evidence that women who drink a lot of alcohol during pregnancy run the risk of giving birth to babies suffering characteristic symptoms including a broad, hairy face and mental retardation. In order to learn about this condition and, eventually, to be able to advise pregnant women on which periods of pregnancy are the most dangerous and how much alcohol, if any, they can drink without endangering the baby, the CSIRO team set up a series of experiments using sheep as models.

The ewes in these experiments ate and drank *ad lib* — in other words, taking as much as they liked whenever they chose. Their only drink was a 10% alcohol solution, roughly equivalent in strength to white wine, and they drank between 1 and 1·5 litres of this a day. Their blood alcohol levels fluctuated during the day between little more than zero and 80–100 mg per 100 ml of blood (0·08–0·1 in the language of motoring law). The ewes showed no unusual behaviour apart from standing quietly for a fairly long time after some meals.

After mating with (sober) rams the ewes experienced normal pregnancies, but they gave birth to abnormally small lambs, some of which also had relatively small brains.

These experiments support the epidemiological evidence for a pronounced foetal alcohol syndrome in humans. The researchers intend next investigating the effects of giving single doses of alcohol to ewes at different stages of pregnancy, to simulate 'binge drinking'. They also want to identify the stage of development at which the foetus is most vulnerable.

Unfortunately, the Division lacks the resources to conduct both iodine and alcohol experiments on sheep simultaneously, but the insights that both programs are giving into the way the foetal brain grows, and into ways in which we can unwittingly but drastically upset that growth, have important implications for medicine and health education.

John Seymour

More about the topic

Production of severe iodine deficiency in sheep using a prepared low-iodine diet. B.J. Potter, G.B. Jones, R.A. Buckley, G.B. Belling, G.H. McIntosh, and B.S. Hetzel. *Australian Journal of Biological Sciences*, 1980, 33, 53–61.

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