# Alcoholic cardiac beriberi

The introduction of dietary changes by Takaki at the beginning of this century had as dramatic an effect in eradicating beriberi from the Japanese navy as had the juice of lemons and limes on the incidence of scurvy in the British navy just over 100 years before. Osler[1] had speculated on the infective versus dietary theories for both beriberi and scurvy, and Eijkman had shown that those who developed beriberi in Java while living mainly on polished rice improved when they were also given the polishings. From the latter Funk later isolated an amine, and it was this "vital amine" which was the first vitamin to be described.

Thiamine pyrophosphate is a coenzyme needed at several stages in the metabolism of carbohydrate. It is found in the husks of rice, the germ of other cereals, and nuts, liver, and yeast. The daily requirement is about 120 $\mu$g/MJ (or about 0·5 mg/1000 kcal)—an amount comfortably contained in a normal Western diet. Thiamine is not stored in the body, and the effects of its deficiency become apparent within a few weeks, particularly if the diet is high in carbohydrate. Wernicke's encephalopathy and the two classic forms of dry and wet beriberi reflect the respective dependence of the nervous system and heart on glucose metabolism. One form of beriberi is often accompanied by features of the other, and the considerable oedema of wet beriberi is often accompanied by peripheral neuritis. Both forms may be accompanied by loss of appetite and gastrointestinal symptoms, together with profound fatigue; in Sinhalese beri means "I cannot."

The only cause of thiamine deficiency likely to be encountered in Britain and the United States is chronic alcoholism. Even in chronic alcoholics, however, the thiamine deficiency diseases are generally considered to be rare, because most of them take enough thiamine-containing foods. A recent report from New Zealand is therefore of considerable interest, since Ikram and his colleagues saw and studied five patients in as many years with alcoholic cardiac beriberi.[2] They speculate that alcoholic cardiac beriberi may be considerably commoner than has been thought.

The traditional view about alcoholic heart disease, well reviewed by Portal,[3] is that there are two separate types. Alcoholic cardiomyopathy is of uncertain cause but is probably due to a specific chronic effect of alcohol on the heart rather than to any dietary deficiency; atrial fibrillation is common, and the characteristic feature is left ventricular failure. Alcoholic beriberi is thought to be much rarer. One of the interesting suggestions of Ikram and his colleagues[2] is that the two types of alcoholic heart disease may occur together, a view that has been postulated by others.[4 5]

The usual features of cardiac beriberi are vasodilatation and consequent high cardiac output. The mechanism is not entirely clear, but accumulation of pyruvic and lactic acids probably plays a part, though their concentrations in the blood are not always raised. Damage to sympathetic nerves may also contribute to the vasodilatation. The extent of oedema is not closely related to the severity of heart failure, and protein deficiency may be present and be a contributory cause.

The typical clinical features therefore occur in alcoholics taking an inadequate diet, particularly in beer drinkers, whose high carbohydrate intake increases the demand for thiamine. Both anorexia and malaise may easily be attributed to alcoholism rather than to thiamine deficiency, and the features of peripheral neuritis are not always present. Pain in the chest is common and occurred in three out of five of the New Zealand patients, all of whom had normal coronary arteriograms. A normal or near-normal electrocardiogram is common, but sometimes the T waves become inverted across the chest leads after thiamine treatment has been started. Non-specific but abnormal histological and electronmicroscopical changes were present in the cardiac biopsy specimens of all five New Zealand patients.

In classic cardiac beriberi in the East right heart failure was more common than left. In alcoholic cardiac beriberi as seen in the West, however, the pattern of left heart failure with dyspnoea, rales, and impaired left ventricular function is more common, so that the typical mode of presentation is biventricular failure with sinus rhythm. The diagnosis may be easily overlooked, especially if features of high cardiac output are absent, as they may be. At present the best diagnostic test for thiamine deficiency is measurement of the transketolase activity[6] in red cells in vitro before and after the addition of thiamine pyrophosphate, but this test is not routinely available in most hospitals in Britain. Measurements of blood concentrations of pyruvic and lactic acids are unreliable as diagnostic guides. Ikram and his colleagues found the response to thiamine given during the course of cardiac catheterisation to be useful, but again this is not a test likely to be available in most hospitals where alcoholics with heart failure present.

The practical implications for clinicians are that they should remember the possibility of thiamine deficiency in patients with unexplained heart failure, particularly in alcoholics, and add thiamine to the conventional treatment. This condition may be more common in Britain than we have realised, particularly with the rising incidence of alcoholism.

PETER CARSON

Consultant Cardiologist,
City General Hospital,
Stoke-on-Trent ST4 6QG

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# Toxicity of pertussis vaccine

"Contact your doctor or clinic for advice about vaccination," say the DHSS posters on whooping cough, challenging parents with the question "Is your baby protected?" What should we tell parents who ask for advice?

Public confidence in pertussis vaccine remains low: the acceptance rate of 80% before the adverse publicity in 1974 has fallen to 30% in recent years and is even below 10% in some parts of the country.[1] The large epidemic of whooping cough in 1977-80, with 32 deaths, had little influence on the vaccination rates, though the alarm to parents, the danger and damage to children, and the effort and expenditure on hospital treatment and home visits were real enough.[1 2] With another epidemic persisting this spring complacency hardly seems likely to be the main cause of the continuing low levels of

vaccination. Doubts about efficacy and safety still linger—such was the impact of the reports on television and in the press in the late 1970s.[3]

The evidence on efficacy is solid. Several reliable studies in the mid-1970s and others in the 1977-80 epidemic have shown that the vaccine in current use in Britain protects 90% or more of those infants who receive the full course of three doses.[4] These estimates are reliable in that the studies were such that the diagnosis was likely to be accurate—in children from whom *Bordetella pertussis* had been isolated, severely ill children, those in hospital, and the very young. Other reports alleging lower levels of protection may be mistrusted because, for example, of unreliable diagnosis or of children who had received only one or two doses of the pertussis component being considered as "vaccinated."

The issue of safety remains. Most of us would accept that no drug is completely safe. A recent American study[5] made a useful distinction between the "less serious" reactions (such as local redness, swelling, pain, fever, and fretfulness) which occurred in over one-third of those vaccinated and the much rarer "more serious" reactions (convulsions and hypotonic hyporesponsive episodes), which were deemed contraindications to further doses of pertussis vaccine. Even more rare are permanent neurological sequelae, as was shown by the vast and careful three-year study in Britain[6] which put the risk at one in 310 000 injections. Both this estimate and those from other less thorough studies "have wide margins of uncertainty."[7] Moreover, even those children regarded as previously normal before developing encephalopathy had a history of previous fits eight times more frequently than did control children; so, "obedience to the contraindications for DPT vaccine . . . is extremely important if attribution of an encephalopathic illness to immunisation is to be avoided."[8]

The rare reaction producing permanent neurological damage, tragic though it may be, should not blind us to the greater dangers of whooping cough itself: deaths alone exceed the numbers of children with permanent damage from vaccination, and an estimate of the respiratory and neurological sequelae of the disease would require a study at least as intensive as that of vaccine encephalopathy. Nevertheless, we need an even safer and a less reactogenic vaccine. The current vaccine is made of whole bacterial cells; it contains lipopolysaccharide endotoxin and its pharmacological effects in animals include histamine-sensitisation, lymphocytosis-promotion, hyperinsulinaemia, and enhancement of immune response by its adjuvant action. Several of these effects may be due to a single substance,[9] which has been called "pertussigen,"[10] but its separation from the protective components of the cell has proved difficult. Human protection requires three surface components (agglutinogens 1, 2, and 3).[11] In the past many countries found that vaccine devoid of factor 3 proved inadequate[12] and Finland has seen the consequences of deficiency in factor 2.[13]

Nevertheless, the future is not without hope. Long ago, the histamine-sensitising factor was shown to be serologically distinct from the surface immunogens[14]; and several countries are investigating a subcellular pertussis vaccine. At Porton Down[15] the emphasis has been on fimbriae and outer membrane protein. Recent studies in our laboratory (unpublished observations) have shown that fimbriate strains are those that produce agglutinogen 2. But where does the other vital immunogen (factor 3) reside? Is outer membrane protein the answer? A subcellular vaccine may not be too far away, but the problems should not be underestimated.[16] Criteria of toxicity and efficacy need to be defined in the laboratory, and large-scale clinical trials would then be necessary to establish that toxicity had been reduced without loss of protection.

Meanwhile, we should not despise the whole-cell vaccine that is available nor the parallel attempts to reduce its toxicity.[17] The adsorbed vaccine recommended by the DHSS not only gives a better immune response than the plain vaccine[18] but also reduces reactions such as fretfulness, crying, and fever.[19] Deep intramuscular injection may lessen the local reaction; but a moderate reaction should be expected as part of the immune response to any bacterial vaccine. And, finally, while observing the contraindications recommended by the DHSS, doctors should not invent extras such as allergies and eczema.

NOEL W PRESTON

Reader in Bacteriology and Director of
Pertussis Reference Laboratory,
University Medical School,
Manchester M13 9PT

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