

This section looks back to some ground-breaking contributions to public health, reproducing them in their original form and adding a commentary on their significance from a modern-day perspective. Michael Krawinkel reviews the identification of kwashiorkor by Cicely D. Williams, which was originally reported in the *Lancet* in 1935.

Kwashiorkor is still not fully understood

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The work chosen as this month's public health classic and reproduced on the following pages is one of the most widely cited papers on childhood malnutrition: in 1935, Cicely D. Williams introduced the West African name kwashiorkor into the scientific literature of nutritional diseases (1).

Williams identified the condition as being associated with the social situation of the affected child in the family: kwashiorkor occurs in the "neglected" child, and thus the main aim of prevention and management should be to overcome this neglect. Most research on nutritional concepts has focused on biomedical aspects — pathogenesis, symptomatology, clinical course, and cell, tissue and organ failure — and appropriate medical care; research on social aspects is far less prominent, even though care for families with a child suffering from kwashiorkor has the potential to prevent and manage the disease effectively. Concentration on pathological and physiological factors and curative medical care takes only a short-term view, and the role of home visits and support has been recognized mainly in respect of preventing relapse. It is perhaps not easy for social paediatric practice to be accepted into scientific research.

Seventy years later, Williams's description of the condition is still valid. The 90% mortality reported in 1935 has declined — but by nowhere near as much as one could have expected. Kwashiorkor still has a high case-fatality rate in many places, and it is still true that most children die after initiation of treatment. This situation requires us to reassess continually our knowledge about the disease and our approach to its management.

Williams described the typical development of the disease, the critical period being the second year of life when other foods are introduced and breastmilk is gradually replaced by a diet of foods suitable for intake and digestion by young children. Among the symptoms mentioned by Williams, peripheral oedema and skin lesions predominate. The clinical appearance of hypopigmentation, hyperpigmentation and desquamation was her main focus for the differential diagnosis, and this view is maintained to the present day. As Latham pointed out, "when 'flaky paint' dermatosis is seen in a malnourished child with oedema, it is pathognomonic of kwashiorkor" (2).

A short account of kwashiorkor research would be incomplete without mentioning the work of Hendrickse and other

researchers working on the possible role of aflatoxins in the pathogenesis of the disease. Their conclusion "clinical observations indicate an association between aflatoxins and kwashiorkor" (3) is still one focus of kwashiorkor research. A recent publication on mice reported "remarkable histopathological changes of the liver in the group fed a low protein diet and aflatoxin B1 when compared with the group fed only a low protein diet" (4). Although this difference lacks statistical significance, it indicates that aflatoxins may play a specific or unspecific role in some children. If exposure to aflatoxins is not a necessary prerequisite for the occurrence of kwashiorkor, it may contribute to the associated liver disease. Since the late 1980s, the pathogenetic impact of oxidative stress on the development of kwashiorkor has become the main focus of research. Jackson studied glutathione (5), and Golden & Ramdath continued by raising awareness of the role of reactive oxygen species in the pathogenesis of kwashiorkor (6). In the 1990s, a group in Heidelberg, Germany, analysed blood antioxidants (G6PDH, glutathione reductase, FAD, and glutathione) and found lowered levels of these major plasma thiols (7). They later reported higher plasma concentrations of biomarkers of oxidant-induced tissue damage in kwashiorkor and demonstrated that the disappearance of clinical signs and symptoms was accompanied by normalization of the biochemical findings (8). These lower antioxidant levels in children with kwashiorkor were confirmed and extended by other investigators (9, 10), and further investigations showed the association between selenium deficiency and congestive heart failure in kwashiorkor (11).

With regard to clinical signs and symptoms, the inflammatory character of kwashiorkor could be related to whole-blood LTE₄ synthesis being increased 3.5-fold in kwashiorkor patients (12) and cytokines such as PGE₂ (13). Future research in this direction may help to close the gap between biochemical findings on cellular level and clinical symptoms.

In 2002 Badaloo and colleagues reported on N-acetylcysteine supplementation in children with kwashiorkor: they observed an earlier and faster recovery in clinical signs and symptoms as well as in glutathione levels (14). Similar findings were reported from a trial in Ghana (K. Becker, personal communication). Jackson asked why the organism is not able to provide cysteine in sufficient amounts to maintain plasma levels and glutathione

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synthesis within normal range (15), which is obviously an important question for further research. In general medical practice — which is often driven more by clinical than by scientific evidence — the beneficial effects of N-acetylcysteine in severe acute liver cell damage (for example, following paracetamol intoxication) indicate that the substrate is well taken up and metabolized even by liver cells under extreme stress (16).

Keeping in mind the high case-fatality rate of kwashiorkor, WHO's concept of ten steps for the management of severe malnutrition (17) represented an important advance. Based on extensive empirical work, especially that of Golden in Jamaica, simple guidelines were developed to improve the quality of case management even in resource-poor circumstances, comprising: the management of hypoglycaemia, hypothermia, dehydration, electrolyte imbalance, infections, micronutrient deficiency, initial and rebuilding nutrition, psychosocial depression as well as the preparation of the follow-up. Instructions to health personnel

explain how to avoid supplying too much sodium by diluting the normal oral rehydration solution and adding sugar, minerals and trace elements. Feeding is designed carefully, with initial restrictions on protein and volume, to avoid overloading the child suffering from more or less symptomatic heart failure.

Implementation of the ten steps represents a truly appropriate technology for the management of this severe and always life-threatening condition. Each point must be dealt with carefully, bearing in mind the individual patient's condition. Improving kwashiorkor management also includes accompanying research on all aspects; work in this direction has been reported by Collins & Sadler (18).

Many parts of the world are still far from achieving safe management of the disease. A new look at the original article by Cicely D. Williams may stimulate further efforts towards preventing and managing kwashiorkor. ■

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