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INFECTION AND KWASHIORKOR*

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Workers with first-hand experience recognize that the overwhelming majority of clinical cases of kwashiorkor represent the effects of both protein malnutrition and infection. The two may be said to be synergistic in their effect, and the net result is more serious than would be the consequences of either infection or protein malnutrition acting alone. Infection may, of course, influence any stage in the development of severe protein malnutrition. It may serve to aggravate the acute episode, interfere with recovery, or even be the final cause of death.

Nearly all reports on kwashiorkor mention that the history of children admitted to the hospital with this syndrome very frequently includes an infectious episode several weeks before. For example, JELLIFFE et al, (1954) in Jamaica, VAN DER SAR (1951) in Curaçao, WATERLOW and VERGARA (1956) in Brazil, PURCELL (1939) in Ghana, PRETORIUS et al, (1956) in South Africa, GERBASI (1956, 1957) in Sicily, DE SILVA et al, (1953) and DE SILVA (1954) in Ceylon, GOPALAN and RAMALINGASWAMI (1955) and also GUPTA (1958) in India, CICELY WILLIAMS (1953) in Africa and Asia, and BEHAR et al, (1956, 1958) in Central America, all stress the high frequency with which diarrhoea of infectious origin is an immediate precipitating cause of clinical kwashiorkor. These authors recognize, however, that other infections may also have a similar effect. Review articles by BROCK and AUTRET (1952), AUTRET and BEHAR (1955), JELLIFFE (1955) and our INCAP group (SCRIMSHAW et al, 1955, 1957 ; BEHAR et al, 1956). have all stressed this point and they, as well as DEMAEYER (1955) in the Belgian Congo, RESTREPO MOLINA (1955) in Colombia, and NETRASIRI (1955) in Bangkok, have called attention to the frequency with which measles is sometimes responsible for a considerable number of cases of kwashiorkor. DEMAEYER also states that tuberculosis may play a similar role (1955). As TROWELL et al, (1954) indicate in their book " Kwashiorkor," almost any infection is capable under certain circumstances of aggravating a pre-existing protein deficiency and producing the clinical signs of kwashiorkor as a result.

Because of the frequency with which intestinal parasites are found in children with kwashiorkor, there has been much speculation regarding their contribution to the development of protein malnutrition. Authors such as the GILLMANS (1951) in Africa, THOMSON (1954) in Malaya, STRANSKY and REYES (1955) in the Philippines, PEÑA CHAVARRIA et al, (1948) in Costa Rica, JELLIFFE (1953) in Western Nigeria, and DE SILVA (1953) in Ceylon, have suggested that the high frequency of ascaris in their kwashiorkor cases must be a contributing factor, and SYMONDS and MOHAMMED (1956) and SYMONDS (1958) believe hookworm in the mother adversely affects lactation performance and thus contributes to infant malnutrition in Trinidad. BROCK and AUTRET, (1952) and PLATT (1957) from their experience in Africa, and GUPTA (1958) in India are representative of the many who feel that parasites are almost always an additional stress factor in the pathogenesis of

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kwashiorkor. It must be noted, however, that in areas in which kwashiorkor is prevalent, intestinal parasites are as common in children of the same age without kwashiorkor as in those with this condition. It is difficult, however to find published records to document this statement for most areas*, and little consideration has been given to the relative intensity of the infection in the two cases.

Mechanisms of the Effects of Infection on Nutritional Status

Infection has an adverse influence on nutritional status in at least three ways, one subjective, one cultural and one physiological. As to the subjective effect, it is scarcely necessary to point out that the child with an infection, particularly when it is an enteric one, experiences anorexia and may fail to eat an adequate diet even when it is offered to him. In our experimental studies if the child with infection is forced to consume the amount of food required, nausea and vomiting are likely to develop and the purposes of the original experiment are obscured. The cultural mechanism is the tendency for the mother to change for the worse the diet of the child with infection, even eliminating all products of animal origin and greatly reducing the amount of solid food given.

The third known mechanism, and one which may be labelled physiological or perhaps metabolic, is the direct effect of infection on the nitrogen balance of the individual. As early as 1884, Müller reported an increased urinary nitrogen excretion over a period of 8 days in a patient with typhoid fever. In 1909, Shaffer and Coleman reported that a net loss of 15 to 20 grammes of nitrogen per day was not unusual in the early stages of typhoid attacks in muscular individuals. Additional data to this effect were published by Rolland (1912), Coleman and Gephart, (1915), Coleman and Dubois (1915) and by Krauss (1926). Krauss also demonstrated reduced nitrogen retention in febrile pulmonary tuberculosis as noted several years earlier by McCann (1922).

Kocher (1914) described a patient with paratyphoid disease who excreted from 14.5 to 16.0 grammes of urinary nitrogen daily with an intake of 2.2 grammes of nitrogen and he obtained similar results in patients with pneumonia, acute polyarthritis, pyelonephritis and erysipelas. Coleman et al, (1922) could not distinguish between the severe adverse effects of erysipelas and typhoid fever on nitrogen retention ; and Cecil et al, (1922) found the nitrogen losses with arthritis to be comparable to the figures mentioned.

The protein losses in meningitis have been shown by Grossman et al, (1945) to be large and prolonged. Even the removal of infected tonsils has been found to bring about a striking improvement in nitrogen retention in children by Johnston and Maroncy (1938) and later by Johnston and Watkins (1954).

Evidence for the adverse effect of infection on nitrogen metabolism is not limited to bacterial infections. Venkatachalam and Patwardhan (1953) have shown clearly that nitrogen absorption is improved when a child's ascaris are removed and, at least in rats, elimination of malaria parasites may improve nitrogen retention according to Dema et al, (1959).

Surprisingly, there are no published records of the effect of virus infections on protein retention. The many reports on association between measles and kwashiorkor, as well as such observations as those of Spicer as long ago as 1892 that children with measles, whooping cough, or malignant varicella often develop xerophthalmia, suggest, however,

*An article entitled " Worm infestations in infants and children of pre-school age in Indore " by J. N. Pohowalla and S. D. Singh has since appeared in the *Indian J. Ped.* **26 :** 459, 1959, which reports the same prevalence of parasites among 727 children with and 995 without malnutrition.

that virus diseases may have as much or more action in precipitating nutritional deficiencies than those of bacterial, protozoan and helminth origin ; certainly they should be thoroughly studied.

In their classic text book, PETERS and VAN SLYKE (1946) discuss the way in which infections may act to bring about a decrease in net nitrogen retention. They suggest that infections cause a toxic destruction of cellular protein which, in turn, results in the increased nitrogen excretion in the urine which is observed in infection. The degree of increased metabolism associated with fever is not sufficient to account for the magnitude of the effect.

Similarly, even in cases of diarrhoea, the effect is not accounted for by decreased absorption, as was recognized as early as the 1915 studies of HOLT et al. More recently, CHUNG (1948) and CHUNG and VISCOROVA (1948) have called attention to the relatively good absorption of nitrogen even in the presence of diarrhoea.

Confirmation of the role of toxic destruction of protein as opposed to the effect of fever and diarrhoea is obtained from the work with turpentine-induced sterile abscesses in dogs (COOK and WHIPPLE, 1918, DAFT et al, 1937, YUILE, et al., 1953).

RECENT INCAP STUDIES

Three years ago, in the course of nitrogen balance studies with a child recovering from kwashiorkor, ROBINSON et al, (1957) in the INCAP laboratories made a urine and faeces collection following one day of mild diarrhoea which occurred on the first day of a 5 day balance period. When the data were subsequently calculated, it was observed that nitrogen retention had dropped from 28 per cent before the diarrhoea episode to -1 during the day of diarrhoea and that recovery was slow, even though there was no recurrence of frank diarrhoea.

During the last 9 months, it has been possible to make a series of observations as to the effect of 7 cases of chicken pox which are summarized in Table I. It will be noted

TABLE I. Effect of Chicken Pox on Nitrogen Balance in Children aged 3—6 years. (Fed 2-3 gm. Protein/Kg, 90 Cal/Kg)*

PC No.	N Retention before illness % of Intake	N Retention at max. effect % of Intake	Duration of effect weeks
82	+ 20	— 17	4†
91	+ 18	— 10	2
92	+ 27	+ 7	2
97	+ 28	— 4	1††
98	—	+ 4	1††
99	+ 21†††	+ 7	1††
102	—	— 10	—

* These intakes usually not achieved during illness due to vomiting.
† Developed Shigellosis.
†† Increased immediately after exanthema.
††† After illness.

that in each of the cases cited, there was a shift from a strongly positive nitrogen balance to a weakly positive or even a negative balance. There are several interesting points about these data that are not immediately apparent from the table. In the first place, an effort was made to maintain the nitrogen and calorie intake equivalent to that during preceding and subsequent balance periods when the child was not ill. Almost without exception, this policy was not successful because the children either flatly refused this quantity of food or vomited part of the diet when food was forced upon them. This confirms a clinical impression that food intake is spontaneously and drastically decreased by the child when he becomes ill, and that any effect of infection in increasing nitrogen excretion is superimposed on the consequences of diminished nitrogen intake.

Another point of very great interest is that the period of maximum effect on nitrogen balance sometimes came not at the time of the greatest symptomatology but in the late prodromal period of the disease. It should also be noted that the duration of the effect of chicken pox on nitrogen balance (1 to 4 weeks) is relatively long, although the latter high figure is probably due to an unknown further complication.

Table II shows the effect of several miscellaneous bacterial infections, each of which was promptly and effectively given antibiotic treatment. Despite this, these diverse infections: shigellosis, asthmatic bronchitis, bronchitis with a probable bronchopneumonia, tonsilitis and staphylococcal abscess, had an influence very similar to that of chicken pox. The diverse bacterial infections all produced a frank decrease in the percentage of nitrogen retained compared to the nitrogen intake. As was observed in the chicken pox cases, most of these bacterial infections adversedly influenced nitrogen balance for a period of at least a week, even though prompt treatment was given.

Increased Susceptibility of Children with Kwashiorkor to Infection

There is little doubt that the biggest hazard which a child with kwashiorkor has to face once electrolyte imbalance has been corrected, is secondary infection. Infections not only interfere with recovery and are responsible for long stationary periods in individuals undergoing treatment, but also are one of the major causes of death in kwashiorkor. The experience in INCAP of Tejada et al, (1956) who found two-thirds of children dying with kwashiorkor to have bronchopneumonia, is not unusual.

Table II. Effect of Various Treated Infectious Processes on Nitrogen Balance in Children Aged 3-6 years (Fed 2-3 gm Protein/Kg, 90 Cal/Kg)*

PC No.	Disease	N Retention before illness % of Intake	N Retention at max effect % of Intake	Duration of effect weeks
82	Shigellosis	+ 20	+ 5	1
91	Asthmatic Bronchitis	+ 18	— 8	1
99	Bronchitis Pneumonia	+ 21	— 24	2
95	Tonsilitis	+ 25†	+ 4	2
95	U.R.I. with Sinusitis	+ 25†	+ 4	1
98	Staph. aureus abscess	—	— 8	—††

* These intakes usually not achieved during illness due to vomiting.
† After illness.
†† Complicated by upper respiratory infection and additional abscess.

Although most authors who discuss kwashiorkor stress the fact that it predisposes to complicating infections, there is no clear explanation, as to the mechanism of this effect. OLARTE et al, (1956) reported from the Hospital Infantil in Mexico that children with third-degree malnutrition showed a definite retardation in the development of antibodies to diphtheria. On the other hand, KAHN et al, (1957) concluded that there was no reduction of isohemagglutinins in severely malnourished children. Research is obviously badly needed on this aspect of the kwashiorkor problem.

CONCLUSION

In the technically underdeveloped areas in which infant and child mortality is particularly high, infection and protein malnutrition combine synergistically to produce a net effect far more severe in its consequences than would result from either the protein malnutrition or the infection occurring alone in the individual or the population. Infection tends to precipitate kwashiorkor by resulting in a decreased food and hence nitrogen intake and increased nitrogen loss in the urine. Furthermore, children with protein malnutrition tend to have more frequent infections and these often prove fatal.

Clinicians and public health workers should recognize that the problem of elevated infant and pre-school mortality must be attacked by programmes designed to combat both protein malnutrition and infection. A programme to control only one of these two factors will always be incomplete and much less effective than when preventive efforts take both into account.

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