CC/NUMBER 52
DECEMBER 29, 1980

# This Week's Citation Classic

Smythe P M, Schonland M, Brereton-Stiles G G, Coovadia H M, Grace H J, Loening W E K, Mafoyane A, Parent M A & Vos G H. Thymolymphatic deficiency and depression of cell-mediated immunity in protein-calorie malnutrition. Lancet 2:939-44, 1971. [Depts. Paediat. and Pathol. and Natal Inst. Immunol., Univ. Natal, and King Edward VIII Hosp,, Durban, South Africa]

**Investigation of the thymolymphatic system and cell mediated immunity in children with protein-calorie-malnutrition (PCM) showed a decrease in: tonsil size, chemical sensitisation of the skin, rate of lymphocyte transformation, the haemolytic serum complement, and thymic and peripheral lymphoid tissue. Lymphopenia below 2,500 prognosed death. In measles less than half had a rash and a giant-celled pneumonia was common. [The *SCI*® indicates that this paper has been cited over 330 times since 1971.]**

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November 11, 1980

"In the early days most research on PCM was centred on supplementary foods and biochemical and electrolyte disturbances. My concern was that despite correction of diet and electrolytes so many children still died. Attendances at autopsies drew attention to the possibility that infection unrecognised clinically could be an important cause of death. Blood cultures identified a high frequency of gram-negative septicaemia as a frequent cause of death, and it was noted that these children were usually afebrile and had little leucocyte response.[1] Taken together with the tendency for Herpes simplex infections to disseminate, the severity of monilial infections, the frequency of a negative tuberculin test n the presence of active tuberculosis, the fulminating course taken by measles, the pattern was that of depressed immunological response, especially of cell-mediated immunity. The final stimulus had a touch of serendipity in that the chance observation that the mitotic figures seen in smears from bone-marrow of children with PCM often showed bizarre configurations and what appeared to be non-dysjunction. When chromosome studies became available an approach was made to one of the coauthors (H.J.G.) to try to ascertain the significance of this observation. Samples were submitted for phytohaemagglutinin stimulation. What was found was the marked inability of lymphocytes to transform.

"One can onty surmise as to why this article has been highly cited. Perhaps because it was multifactorial, drawing together clinical, immunological, and pathological observations, including a number of observations made by earlier workers into a coherent picture of significant immunological depression. Perhaps it was opportune, coming at a time when there was widespread interest both in immunology and nutrition. Perhaps it was a product of clinical observations, coupled with advances in laboratory investigations. Of interest is how pure clinical observations can precede scientific explanation. For years one had taught that children suspected of active tuberculosis with a negative tuberculin test should have active anti-tuberculosis treatment. If after three weeks' treatment the tuberculin test remained negative treatment could be stopped, as by that time tuberculin sensitivity would have been reestablished. This is the precise period found for delayed hypersensitivity to be reestablished in PCM.

"The research was carried out in the departments of paediatrics and pathology and the Natal Institute of Immunology of the University of Natal and King Edward VIII Hospital, Durban, South Africa. All the coauthors made significant contributions. Particularly helpful was the work done on lymphocyte transformation (H.J.G.), the serology (G.H.V.), and the detailed pathological studies (M.S.)."

1. **Smythe P M & Campbell J A H.** The significance of ihe bactcraemia of kwashiorkor. *S. Afr. Med. J.* **33**:777, 1959.