The absence of B substance from the saliva of Miss X, together with the eventual disappearance of nearly all of the cells possessing the weak B antigen, are facts which support the hypothesis of an acquired B antigen. The family study, unfortunately, contributes very little to the investigation beyond establishing that neither the brother nor sister possesses the same antigen.

If the idea of an acquired B antigen is accepted, then the reactions of Miss X's anti-B agglutinins become interesting. It has been shown that her cells react with a specific component of anti-B sera. The absence of any reactions between her cells and her own serum suggests strongly that her serum lacks this specific component. Two possible explanations for the absence of this fraction must be considered: (1) *in vivo* absorption by her own cells, and (2) depression of her antibody-producing mechanism.

Miss X cells cannot be shown to be sensitized or coated with antibody by any technique. Furthermore, the post-mortem serum fails to react with the cells in the original sample. From this it is clear that the post-mortem serum still lacks the fraction that would agglutinate her own cells. As the post-mortem sample is almost free from weak B cells that could absorb her own antibody, it follows that auto-absorption is unlikely to be the explanation of the missing fraction. It appears most probable that her red cells have been modified and acquired a B antigen. This antigen in turn has caused a modification of her anti-B agglutinins, thus preventing a reaction with her own cells.

The chimeras that have been reported (Dunsford *et al.*, 1953; Booth *et al.*, 1957; Nicholas *et al.*, 1957) show that exposure to a foreign antigen early in foetal life can inhibit antibody production thereafter. Dunsford and Stacey (1957) have reported partial breakdown of this antibody suppression in a chimera possessing A and O red cells. Anti-A agglutinins developed in this case that were not, however, auto-agglutinating. It would appear that Miss X, whose case is here reported, confirms their supposition of immunological tolerance and establishes that foreign antigens may be tolerated, even in the presence of "homologous" antibody, providing the "foreign" antigen is present in the individual's own cells.

Summary

A new type of weakly reacting B antigen is described. B substance was absent from the saliva and anti-B agglutinins were present in the serum. Serological evidence is given to show that this antigen probably developed as an acquired character, and a technique is described by which a B antigen can be produced *in vitro* in group A₁ cells. The anti-B agglutinins in the serum did not react with the acquired weak B antigen in the cells, and possible causes for this are discussed.

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PURPURA IN KWASHIORKOR

BY

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Purpura is a well-known though uncommon clinical finding in children suffering from kwashiorkor (malignant malnutrition, infantile pellagra), the haemorrhagic spots in these patients occurring principally over the clavicles, lower abdomen, and groin, occasionally coalescing into large purplish blotches. It is briefly referred to by some authors in the discussion of the dermatosis of malnutrition (Hanafy, 1948; Achar, 1950; Trowell *et al.*, 1954), but little work has been done to elucidate the cause of the purpuric eruption, and for the most part it appears to have been accepted as a manifestation of rupture of fragile vessels in poorly nourished tissues.

At this hospital we see from 600 to 800 cases of severe kwashiorkor annually, and most of these patients are between 6 months and 3 years old. About 80% of these children suffer from primary malnutrition, being weaned on to a diet of maize porridge and water at an early age. In the remaining 20% chronic debilitating diseases, most commonly tuberculosis and salmonellosis, are present in addition to malnutrition. Parasitic diseases such as malaria and hookworm are not endemic in this area. Mild iron deficiencies and megaloblastic anaemia with haemoglobin levels of about 8 g./100 ml. are not uncommon, but purpura is relatively rare, being seen in 3–5% of patients suffering from kwashiorkor.

It has been our impression that the purpura of malnutrition is rarely associated with obvious haematological defects, but that there appears to be an undue preponderance of tuberculosis and salmonellosis in such patients. It was with a view to elucidating this observation that we undertook the following investigation.

Materials and Methods

We investigated 23 severely malnourished children suffering from purpura who were admitted to our wards over a period of nine months. All suffered from severe malnutrition with evidence of nutritional oedema or acute nutritional dermatosis or both.

The following investigations were carried out in all cases: the bleeding-time was determined by Duke's method and the clotting-time by the method of Lee and White; haemoglobin estimation, prothrombin index (Quick one-stage method), and bile and broth cultures were performed, using venous blood; all patients were subjected to tuberculin-testing with second-strength purified protein derivative, and their chests were radiographed; rectal swabs were taken and cultured for

Purpura in Kwashiorkor

Case No.	Age (Mths)	Sex	Weight		Hb (g./100 ml.)	Platelets (per c.mm.)	Prothrombin Index %	Bleeding-time (Minutes)	Clotting-time (Minutes)	Pathogens in Stools	Blood Culture	Mantoux Test	Chest X-ray	Bone Marrow	Summary of Diagnosis
			lb.	kg.											
1	13	M	14	6.4	6.4	>150,000	100	4	5	Nil	Salm.	Neg.	Normal	—	K. and S.
2	22	M	23	10.4	5.4	>150,000	90	2	4	"	Neg.	Neg.	Tuberculous broncho-pneumonia	—	K. and P.T.
3	15	M	15	6.8	11.7	>150,000	84	2	4½	"	"	"	"	—	"
4	12	M	12	5.4	10.6	>150,000	91	2	3	"	"	Neg.	Normal	—	Kwashiorkor
5	8	M	8½	3.9	10.8	>150,000	100	1	4	"	"	"	"	—	"
6	23	M	15	6.8	9.4	>150,000	95	1	2½	Salm.	"	"	"	—	K. and S.
7	19	M	17	7.7	10.6	>150,000	54	4	4	Nil	"	"	"	—	Kwashiorkor
8	4	M	5½	2.5	15.2	>150,000	95	1½	3½	Salm.	"	"	"	—	K. and S.
9	18	F	19	8.6	11.9	20,000	68	10	4	Nil	"	"	"	Few megakaryocytes	K. and Thr.
10	7	M	9	4.1	8.9	>150,000	63	5	5	"	"	"	"	—	Kwashiorkor
11	30	F	25	11.3	4.0	25,000	95	9	3	"	"	"	"	Few megakaryocytes	K. and Thr.
12	15	M	13	5.9	8.0	>150,000	93	1½	4	"	"	Pos.	Tuberculous broncho-pneumonia	—	K. and P.T.
13	8	M	10	4.5	11.2	>150,000	80	4	5	"	Salm.	Neg.	Normal	—	K. and S.
14	8	M	11	5.0	13.1	>150,000	74	3	4½	Salm.	Neg.	"	"	—	"
15	14	F	7½	3.4	9.4	>150,000	62	2	2	Nil	Salm.	"	"	—	"
16	13	F	11	5.0	11.5	>150,000	68	2	2½	"	Neg.	"	"	—	Kwashiorkor
17	14	M	15	6.8	11.4	>150,000	78	1½	5	"	"	Pos.	Miliary tuberculosis	—	K. and M.T.
18	24	M	20	9.1	10.1	>150,000	73	2½	3	"	Salm.	Neg.	Normal	—	K. and S.
19	60	F	26	11.8	9.2	>150,000	92	1½	3	"	Neg.	Pos.	Tuberculous broncho-pneumonia	—	K. and P.T.
20	36	M	20	9.1	9.5	>150,000	63	2	2	"	"	"	Miliary tuberculosis	—	K. and M.T.
21	24	M	17	7.7	9.9	>150,000	74	3	2	Salm.	"	Neg.	Normal	—	K. and S.
22	10	M	10	4.5	10.2	>150,000	93	2½	4	Nil	"	Pos.	Tuberculous broncho-pneumonia	—	K. and P.T.
23	18	M	15	6.8	8.7	>150,000	76	3	3	"	"	"	"	—	"

K.=Kwashiorkor. M.T.=Miliary tuberculosis. P.T.=Pulmonary tuberculosis. S.=Salmonellosis. Thr.=Thrombocytopenia.

pathogens; iliac crest bone-marrow punctures were carried out in two patients in whom platelet deficiencies were found

Results of Investigation

The age of the patients in this investigation ranged from 5 months to 8 years; however, 21 of the 23 were from 7 months to 3 years old (see Table). There were 18 males and 5 females. All were severely malnourished, 13 were oedematous, and 17 had acute nutritional dermatosis; 10 were severely wasted and 6 had marked hepatomegaly.

The following haematological abnormalities were the only ones observed in this series. Bleeding-times were abnormally prolonged in two patients, with associated thrombocytopenia. Both had hypoplasia of the bone marrow with very few megakaryocytes. One of these children had received chloramphenicol previously. The marrow of one child returned to normal after a prolonged stay in hospital. The other child died of cerebral haemorrhage.

In the remaining 21 cases bleeding-times and platelet counts were normal; clotting-times were normal in all 23 cases. Prothrombin indices were less than 100% in 21 cases, the lowest level being 54%.

Evidence of associated infection with *Mycobacterium tuberculosis* or salmonellae was found in 16 of the 23 patients. Eight of these had tuberculosis, with positive tuberculin tests and active pulmonary lesions on x-ray examination, two being miliary in type. In the remaining eight patients, pathogens of the *Salmonella* group were isolated—four on blood culture and four in cultures from rectal swabs. Those isolated on blood culture were *Salm. typhosa*, *Salm. typhimurium*, *Salm. San Diego*, and *Salm. Adelaide*; those isolated on rectal swab culture were *Salm. Kentucky*, *Salm. Johannesburg*,

Salm. Aberdeen, and *Salm. Newport*.

No treatment had been given to the patients with tuberculosis or salmonellosis before the purpuric rash was observed. Of the total 23 children investigated, 7 died.

Discussion

In only 2 of the 23 patients suffering from kwashiorkor with purpura was there any obvious haematological abnormality to explain the bleeding phenomenon. These were the two children with thrombocytopenia due to bone-marrow hypoplasia. In one of these, hypoplasia was probably due to the chloramphenicol toxicity; in the other the aetiology was unknown. In all other cases drugs could be excluded as an aetiological factor. In the remaining 21 children the bleeding- and clotting-times were within normal limits, platelet counts were normal, and the only abnormality detected was moderate depression of the prothrombin index. However, the latter is the usual finding in kwashiorkor; thus in a consecutive series of 25 children suffering from severe kwashiorkor but without purpura the prothrombin index was equally depressed (see Fig.). Merskey and Hansen (1955),

Prothrombin indices of 23 cases of purpura associated with kwashiorkor (A) and of 25 consecutive cases of kwashiorkor without evidence of purpura (B).

investigating purpura in kwashiorkor, found that the prothrombin index was almost invariably reduced, this reduction apparently being due to deficiency of factor VII or prothrombin itself

The striking feature in our investigation was the high incidence of associated tuberculosis and salmonellosis. Among our admissions of kwashiorkor in 1956 there were only 8% with salmonellosis and 10% with pulmonary tuberculosis. In the present series, 16 of 23 (70%) patients had severe pulmonary tuberculosis or salmonella septicaemia or enterocolitis. This confirms our previous clinical observations extending over several years and strongly suggests some causal relationship between the purpura of kwashiorkor and these infections

The association of tuberculosis and purpura, mainly in adults, is well described. In most instances the tuberculosis is of the miliary type, with bone-marrow infiltration causing aplasia or myelofibrosis with thrombocytopenia (Chapman and Whorton, 1946; Crail *et al.*, 1948; Gardner and Mettier, 1949; Ellman and Johnson, 1952; Fountain, 1954). Tuberculosis as a cause of purpura, without haematological abnormalities, as in our patients, is also described. Ellman and Johnson (1952), reviewing the literature, found 46 such cases. Most of these were cases of pulmonary tuberculosis without miliary spread. These authors concluded that where purpura occurs with tuberculosis there is an aetiological relationship between the two conditions, except in a few instances where a chance association cannot be excluded. Wintrobe (1951) enumerates the tubercle bacillus as a possible exciting cause of allergic purpura. Purpura following Mantoux-testing has been described (Wright and Bacal, 1937).

There is scanty reference to the association of purpura and salmonellosis. Eisenberg *et al.* (1958), discussing clinical and microbiological aspects of salmonellosis, do not list purpura as a clinical feature. Felsen (1945) does not mention the association of purpura and salmonella enterocolitis. Septicaemia is not commonly believed to be a phase of salmonella infections apart from typhoid and typhimurium, but two of the four infections isolated on blood culture in our series were *Salm. San Diego* and *Salm. Adelaide*. It is probable that the purpura occurred as a manifestation of salmonella septicaemia. Rolleston and Molony (1912), writing on cachectic purpura in children, found an association of the purpura with "infective" diarrhoea in 11 cases. They isolated *Bacillus enteritidis* (*Salm. enteritidis*) from heart blood in only one case at post-mortem examination, but suggested that cachectic purpura was commonly due to this type of haemic infection. It would appear that in our African community we may well be seeing cachectic purpura such as was seen by Rolleston and Molony in children in England during the early part of this century against a similar background of malnutrition and complicated by similar infections. Since then, however, the prognosis of "cachectic" purpura has improved. All their cases were fatal, whereas 7 of our 23 patients (30%) died. The overall mortality of kwashiorkor in our unit is 20%, and this suggests that, in kwashiorkor, purpura is an indication of poor prognosis.

Summary

An investigation into the purpura of kwashiorkor is described.

Of 23 African children investigated, only 2 had prolonged bleeding-times, thrombocytopenia, and megakaryocytopenia to explain the bleeding phenomenon. The rest had normal bleeding-times and platelet counts. All had normal clotting-times. Practically all had low prothrombin indices, but so had a control group of 25 cases of kwashiorkor without purpura.

Sixteen (70%) of the patients were found to be suffering from tuberculous or salmonella infection, an association far in excess of the overall incidence of these infections in our patients with kwashiorkor. It is felt that this suggests a causal relationship between these infections and the purpura of kwashiorkor.

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The Social Medicine Research Unit of the Medical Research Council and the General Register Office jointly carried out a statistical inquiry into deaths in infancy of children born in 1949 and 1950 in England and Wales. The main results have been published in separate papers, but the basic data are now presented in a single volume—*Social and Biological Factors in Infant Mortality*, by J. A. Heady, M.A., and M. A. Heasman, M.R.C.S., L.R.C.P., D.P.H. (H.M.S.O., £1). Detailed tables provide data on the births in 1949 and 1950 according to the age of the mother and her parity, and on the stillbirths and deaths in infancy of children born in these years according to the age and parity of the mother and the social class of the father. Other factors in analysis include the area where the parents lived; the number of previous children lost by the mother, and the duration of her marriage. Causes of death are analysed and data are also given on multiple and illegitimate births.