Summary

During a two-year period (1955-6) 1,565 cases of kwashiorkor were studied in the paediatric unit of the King Edward VIII Hospital, Durban.

The clinical criteria for the diagnosis of kwashiorkor are stated. No case presenting predominantly with emaciation was included in this series.

A marked seasonal incidence in Durban is noted, the disease being far more common during the summer months.

The common clinical findings and their incidence are described. Special attention has been drawn to the prevalence (20% of cases) of ulceration or actual tissue necrosis (possibly "nutritional gangrene") and of the increasing incidence of ulcerating corneal lesions in Durban.

The very high incidence of associated infections is stressed.

While detailed haematological and biochemical investigations were not possible in all instances, the findings are given in a considerable number of cases investigated.

The frequency of anaemias (including megaloblastic types) is discussed in the light of available literature, the slow erythropoietic recovery being characteristic.

The bad prognostic signs of bradycardia and elevation of the level of serum bilirubin are noted.

Reasons for the high incidence of kwashiorkor in Durban are discussed. The high death rate, due mainly to associated infections in an eminently preventable condition, is deplored.

A brief description of the treatment prescribed in this unit is given.

We wish to record our thanks to Dr. H. L. Wallace, head of the Department of Paediatrics, University of Natal and King Edward VIII Hospital, Durban, and Dr. Pauline Klenerman, in whose wards the majority of cases were treated; to Professor E. B. Adams and Professor T. Gillman for a great deal of helpful advice and encouragement; to Professor J. Wainwright and Dr. G. Roach for the pathological and biochemical studies; Dr. M. Hathorn for help in the preparation of the tables; and to Mrs. P. Kruger for the photography. Finally we thank Dr. S. Disler, medical superintendent, King Edward VIII Hospital, Durban, for facilities.

REFERENCES

- Achar, S. T. (1950). *Brit. med. J.*, **1**, 701.
 — and Benjamin, V. (1953). *Indian J. Child Hlth*, **2**, 1.
 Adams, E. B. (1954). *Brit. med. J.*, **1**, 537.
 Altman, A. (1948). *Clin. Proc.*, **7**, 32.
 — and Murray, J. F. (1948). *S. Afr. J. med. Sci.*, **13**, 91.
 Blumenthal, C. J. (1950). *S. Afr. med. J.*, **24**, 191.
 Brock, J. F. (1954). *Med. Ill. (Lond.)*, **8**, 827.
 — (1955). *Voeding*, **16**, 169.
 — and Autret, M. (1952). *Bull. Wld Hlth Org.*, **5**, 1.
 — and Hansen, J. D. L., Howe, E. E., Pretorius, P. J., Davel, J. G. A., and Hendrickse, R. G. (1955). *Lancet*, **2**, 355.
 Dean, R. F. A., and Schwartz, R. (1953). *Brit. J. Nutr.*, **7**, 131.
 — (1954). *Courier*, **4**, 293.
 Finberg, L., and Harrison, H. E. (1955). *Pediatrics*, **16**, 1.
 Gelfand, M. (1946). *Clin. Proc.*, **5**, 135.
 — (1956). *Cent. Afr. J. Med.*, **2**, 425.
 Gillman, T., and Gillman, J. (1945a). *Arch. intern. Med.*, **76**, 63.
 — (1945b). *J. Amer. med. Ass.*, **129**, 12.
 Gillman, J., and Gillman, T. (1951). *Perspectives in Human Malnutrition*. Grune and Stratton, New York.
 Gomez, F., Galvan, R. R., and Munoz, J. C. (1952). *Pediatrics*, **10**, 513.
 Hansen, J. D. L. (1956). *S. Afr. J. Lab. clin. Med.*, **2**, 206.
 Jelliffe, D. B. (1953). *J. trop. Med. Hyg.*, **56**, 104.
 Janssen, E., and Le Roux, J. S. (1950). *S. Afr. J. clin. Sci.*, **1**, 100.
 Kahn, E., Wayburne, S., Shnier, M. H., Stein, H., Cronje, R. E., Freiman, I., Levin, S. E., Orska, I., Reef, I., and Theunissen, J. (1958). *Med. Proc.*, **4** (10), 253.

- Kark, S. L. (1943). *S. Afr. J. med. Sci.*, **8**, 106.
 Kinnear, A. A., and Pretorius, P. J. (1957). *S. Afr. med. J.*, **31**, 174.
 Klenerman, P. (1950). *Ibid.*, **24**, 891.
 Oomen, H. A. P. C. (1954). *Brit. J. Nutr.*, **8**, 307.
 Pretorius, P. J., Hansen, J. D. L., Davel, J. G. A., and Brock, J. F. (1956). *S. Afr. med. J.*, **30**, 447.
 Suckling, P. V., and Campbell, J. A. H. (1957). *J. trop. Pediat.*, **2**, 173.
 Trowell, H. C. (1937). *Arch. Dis. Childh.*, **12**, 193.
 — (1944). *Clin. Proc.*, **3**, 381.
 — (1954). *Ann. N.Y. Acad. Sci.*, **57**, Art 6, 722.
 — and Davies, J. N. P. (1952). *Brit. med. J.*, **2**, 796.
 — and Dean, R. F. A. (1952). *Ibid.*, **2**, 798.
 — (1954). *Kwashiorkor*. Arnold, London.
 — and Simpkins, M. J. (1957). *Lancet*, **2**, 265.
 Urbach, E., and Le Winn, E. B. (1946). *Skin. Diseases, Nutrition and Metabolism*. Grune and Stratton, New York.
 Walt, F., Wills, L., and Nightingale, R. P. (1950). *S. Afr. med. J.*, **24**, 920.
 — Holman, S., and Hendrickse, R. G. (1956). *Brit. med. J.*, **1**, 1199.
 Williams, C. D. (1933). *Arch. Dis. Childh.*, **8**, 423.
 — (1935). *Lancet*, **2**, 1151.
 Woodruff, A. W. (1955). *Brit. med. J.*, **1**, 1297.

AN ABNORMALITY OF BLOOD LIPIDS
IN HEREDITARY SPHEROCYTOSIS

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Several metabolic differences between blood of patients with hereditary spherocytosis and blood of normal subjects have been described; these include differences in inorganic phosphate levels, sodium transport, and intermediary carbohydrate metabolism (see review by Pranker, 1959). It appears likely that these changes are secondary to a defect in the red-cell membrane which is manifested by the reduced surface area to volume ratio in spherocytes. The primary genetically controlled defect is not yet known, but the striking abnormality in shape of the red cells suggests that a component of the cell membrane, possibly a phospholipid, may be involved. For this reason we have investigated the phosphatide composition of spherocytes, as compared with normal cells, as well as the rate of incorporating of ^{32}P into phosphatides of normal and abnormal blood cells. A characteristic difference between normal and spherocytic blood lipids has been revealed, and this difference may possibly explain the development of spherocytosis in susceptible subjects.

Materials and Methods of Study

Blood was obtained from two young women with typical hereditary spherocytosis and family histories of the condition; one subject had had a splenectomy. Normal and abnormal bloods were incubated with ^{32}P -orthophosphate in citrate-dextrose for five hours at 37°C . as previously described (Lovelock *et al.*, 1959). The cells were separated from plasma and extracted with methanol-chloroform (Bligh and Dyer, 1959). The lipids recovered were separated by chromatography on silicic-acid-impregnated paper (Marinetti *et al.*, 1957), identified by their R_f value and staining behaviour, and analysed quantitatively by determining the phosphorus

present in each component. The ^{32}P activities of the total lipids and each phosphatide component were also determined, and specific activities were calculated. The fatty-acid composition of the total lipids was determined by gas-liquid chromatography (James, 1960).

Observations

The main results were summarized in the Table. The total phosphatide content per millilitre of blood was lower in spherocytes than in normal cells, but cell

Phosphatides of Normal and Spherocytic Blood Cells

Component	Phosphatide Concentration in Molecules/ μ^2 Cell Surface ($\times 10^6$)		Composition % of Total Lipid		Sphering Action
	N.	Sph.	N.	Sph.	
Total phosphatides	8.2	9.7	100	100	
Phosphatidyl inositol + lysolecithin	0.27	0.33	3.3	3.5	+
Sphingomyelin + lysophosphatidyl ethanolamine	1.9	3.2	23	33	+
Lecithin	3.7	4.2	45	44	—
Phosphatidyl ethanolamine	2.3	1.8	28	19	
Phosphatidic acid	0.06	0.1	0.7	1.1	

N. = Normal. Sph. = Spherocytes.

surface concentration of phosphatides, which is a more meaningful expression, was actually slightly higher in spherocytes than in normal cells. This result is not in agreement with the old but much-quoted evidence of Erickson *et al.* (1937) that the phosphatide concentration in normal and spherocytic cells is the same per unit surface area. The fatty acid composition of the total lipids or spherocytes did not differ significantly from that of normal cells, and will not be discussed in detail. Incorporation of ^{32}P into phosphatides was greater in abnormal than in normal blood cells. This may be due partly to the smaller phosphatide pool and partly to the presence of a slight but significant leucocytosis in the spherocytic blood, since leucocytes are responsible for most of the synthesis of phosphatides by blood cells *in vitro* (Rowe *et al.*, 1960; Buchanan, 1960). In any case, this result appears to exclude any defect in overall synthesis or turnover of cell phosphatides in hereditary spherocytosis.

The qualitative composition of the phosphatides appeared to be identical in both abnormal and normal cells, but the spherocytes were found to contain a significantly higher concentration of the lysophosphatidyl ethanolamine + sphingomyelin fraction, and a correspondingly lower concentration of phosphatidyl ethanolamine (see Table). Since sphingomyelin could not be separated from lysophosphatidyl ethanolamine by the chromatographic system used, it is difficult to establish whether the observed increase in the sum of these components corresponded to an increase in either one or both of them. However, the fact that the increase was exactly balanced by a decrease in phosphatidyl ethanolamine suggests that lysophosphatidyl ethanolamine is the component involved.

To ascertain whether the higher concentration of lysophosphatidyl ethanolamine in spherocytic blood might be related to the change in red-cell shape, the component phosphatides of normal and abnormal cells were separated chromatographically and eluted from the paper. Each component was then suspended in normal serum to give a final concentration above normal of 100 μg . of lipid P per ml. (one and a half to six times the normal concentration of serum components). Normal red cells were added to the sera

in silicone-treated tubes in a ratio of 2:3 (v/v), and the suspension incubated for six hours at 37° C. with occasional agitation. The cells were examined in freshly prepared wet film preparations by phase-contrast microscopy, by which the overall shape is well shown. The only phosphatide components which produced significant spherizing of red cells were those containing lysolecithin and lysophosphatidyl ethanolamine. A pure preparation of sphingomyelin produced no spherizing. None of the preparations showed detectable haemolysis.

Comment

The experimental results here outlined suggest that there is no overall limitation of phosphatide synthesis or turnover in blood cells in hereditary spherocytosis, nor is there any unusual fatty-acid synthesis. However, there is an abnormality of phosphatide synthesis in the abnormal blood cells which is manifested by low levels of phosphatidyl ethanolamine and accumulation of lysophosphatidyl ethanolamine. Two interpretations of these findings can be offered. According to the first, the lysophosphatidyl ethanolamine is produced from phosphatidyl ethanolamine by the action of an enzyme, phosphatidase A, present in spherocytic blood. On this basis, however, it is difficult to explain why spherocytes have a higher concentration of lysophosphatidyl ethanolamine than normal. Moreover, this enzyme is known to act much more rapidly on lecithin, forming lysolecithin, than it does on lysophosphatidyl ethanolamine.

The second interpretation, which seems to us the more likely, is based on the hypothesis that phosphatidyl ethanolamine is synthesized normally as follows:

If in hereditary spherocytosis there is a partial block of the last step, this would account for accumulation of the lyso-compound and diminution of the phosphatidyl ethanolamine. It is obvious that the metabolic block cannot be complete, nor would a complete block be expected, since subjects with hereditary spherocytosis, being heterozygous, have one normal gene as well as one abnormal gene at the locus concerned.

The experiments with phosphatides added to normal serum suggest that lysolecithin and lysophosphatidyl ethanolamine are the only two phosphatides (in concentrations less than 10 times the physiological levels in serum) capable of inducing significant spherizing of cells. This result might be expected since both compounds are surface-active and in higher concentrations are strongly lytic. The fact that lysolecithin is present in similar low concentrations in normal and abnormal cells excludes the possibility that this compound plays a part in hereditary spherocytosis, as was once thought (Bergenheim and Fähræus, 1936). However, the significantly higher concentration of lysophosphatidyl ethanolamine in the abnormal blood cells may well be related to the fact that as the erythrocytes become older they assume the spherical shape and are segregated by the spleen. If the concentration of lysophosphatidyl ethanolamine is high in the spleen, especially the abnormal spleen, there might be an explanation for the finding that incubation of erythrocytes in the spleen predisposes the cells to lysis, despite the presence of adequate glucose (Motulsky *et al.*, 1958); we hope to investigate this point further, and offers of fresh splenic material from normal and spherocytic subjects would be welcome.

The question arises whether the metabolic differences between spherocytes and normal erythrocytes summarized by Pranker (1959) are primary or whether they follow from the defect of lipid synthesis described above. We favour the latter interpretation, since alterations in sodium and phosphate ion transport could well result from an abnormal membrane containing a higher proportion of a surface-active component (lysophosphatidyl ethanolamine) than usual. If the abnormality in phosphatide synthesis were secondary it would be remarkable if only a single pair of components were affected (lysophosphatidyl and phosphatidyl ethanolamine), all other phosphatides being present in identical proportions. We therefore conclude that the most likely primary genetic defect in hereditary spherocytosis is in the final stage of synthesis of phosphatidyl ethanolamine, all other observed differences in spherocytes being a consequence of this metabolic lesion. The lesion is shown by leucocytes synthesizing phosphatides *in vitro* and would probably be manifested in many other bodily organs *in vivo*, especially the spleen.

Summary

The phosphatides and their fatty acids from blood cells of normal and hereditary spherocytic subjects have been analysed. Incorporation of ^{32}P -orthophosphate into phosphatides of normal and abnormal blood cells incubated *in vitro* has also been studied. There is no limitation of overall phospholipid synthesis or turnover, or difference from normal of fatty-acid synthesis, in hereditary spherocytosis. However, the spherocytic cells have a significantly higher proportion of lysophosphatidyl ethanolamine, and a significantly lower proportion of phosphatidyl ethanolamine, than normal cells. Incubation of normal cells in serum to which lysophosphatidyl ethanolamine had been added led to a significant amount of spherizing. It is concluded that the primary genetically controlled abnormality in hereditary spherocytosis probably lies in a partial block in the enzymic system for conversion of lysophosphatidyl ethanolamine to phosphatidyl ethanolamine. All other observed differences between normal and spherocytic cells could be secondary to such a defect.

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REFERENCES

- Bergenheim, B., and Fähræus, R. (1936). *Z. ges. exp. Med.*, **97**, 555.
 Bligh, E. G., and Dyer, W. J. (1959). *Canad. J. Biochem.*, **37**, 911.
 Buchanan, A. A. (1960). *Biochem. J.*, **75**, 315.
 Erickson, B. N., Williams, H. H., Hummel, F. C., Lee, P., and Macy, I. G. (1937). *J. biol. Chem.*, **118**, 569.
 James, A. T. (1960). *Meth. biochem. Anal.*, **8**, 1.
 Lovelock, J. E., James, A. T., and Rowe, C. E. (1959). *Biochem. J.*, **74**, 137.
 Marinetti, G. V., Erbland, J., and Kochen, J. (1957). *Fed. Proc.*, **16**, 837.
 Motulsky, A. G., Casserl F., Giblett, E. R., Broun, G. O., jun., and Finch, C. A. (1958). *New Engl. J. Med.*, **259**, 1215.
 Pranker, T. A. J. (1959). *Brit. med. Bull.*, **15**, 54.
 Rowe, C. E., Allison, A. C., and Lovelock, J. E. (1960). *Biochim. biophys. Acta*, **41**, 310.

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ROLE OF THE PLASTIC SURGEON AND PSYCHIATRIST IN THE SURGERY OF APPEARANCE*

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Plastic surgeons and psychiatrists share a joint awareness of the inseparably close relationship which links facial appearance, bodily proportion, and the overall function and structure of human beings to their morale and personal identification, including their sexual fantasies, hopes, and fears. Men and women are themselves innately conscious of this aspect of the inevitable interdependence of mind and body, and it is often their search for happiness or peace of mind, at least as much as considerations of physical comfort or convenience, which lead them to seek bodily reconstruction of any kind.

The implications of this are surely that we must pay attention to the state of mind as well as to the bodily structure of all who seek our aid in the field of plastic surgery. Only in this way will we recognize the opportunities, as well as the limitations, which may be involved when an individual seeks a structural change against a setting of emotional disturbance.

We submit that there is a need for an agreed classification in basic terms of this problem of the reactions to disfigurement. It is a problem which does in fact impinge upon nearly every plastic operation, and has long been recognized as of importance by every plastic surgeon. This recognition has largely concerned the occasional major complications of a plastic operation in which latent psychiatric disorder has been overtly and explosively released, for example, by an operation on the nose.

TABLE I.—Non-Psychotic Reactions to Disfigurement

Mental Health	Degree of Objective Disability or Disfigurement	Disposal	Reactions
(1) Normal	Slight to grave	Plastic repair	Normal, but depend on: standard of result; I.Q. of patient; and life situation of patient
(2) Emotional instability; immature personality	May not even exceed normally acceptable limits	Psychiatric assessment <i>re</i> indications for surgery advisable in these cases. Decision should be based on (1) practicability of acceptable improvement; (2) patient's predicted capacity to withstand failure	Plastic result can be good in selected cases. Occasionally a plastic repair can contribute to overall recovery of morale
(3) Grave neurosis	Illness fastened on purely marginal disfigurement or change in anatomy		

Classifications of Reactions.—The simplest and most practical classification is to divide the reactions into (1) non-psychotic (or sane) reactions (Table I), of which there seem to be three main groups; and (II) psychotic reactions (or insane reactions), of which it is possible to distinguish two main groups (Table II).

*Based on a joint communication to the International Congress of Plastic Surgery at the Royal College of Surgeons of England on July 17, 1959.