Cell Membrane Anomaly Impeding Cell Division

'Hempas' (Congenital dyserythropoietic anaemia, type 2)[1,2] is a congenital disease characterized by inefficient erythropoiesis and multinuclearity of the erythroblasts in bone marrow (Figure 1). The erythrocytes are strongly agglutinated by anti-i antibodies and are lysed by acidified normal serum. The dissociation between the nuclear and the cellular division, observed in the erythroblasts of these patients, may be of physiopathological importance.

A bone marrow aspirate of 1 patient (case 2) and peripheral blood of 3 patients (cases 1, 2 and 3) previously described by us[3] were subjected to electron microscopic investigation. The samples were fixed for 60 min in 5% phosphate buffered glutaraldehyde and post fixed in 1% MILLONIG's[4] Os O4 for 75 min both procedures at 4 °C. After ethanol dehydration the cells were embedded in Epon[5].

In the bone marrow numerous binucleated red cell precursors were observed. The periphery of most erythroblasts shows an abnormality: an additional linear structure following the inside of the cell membrane, mostly at a distance of 400–600 Å (Figure 2). On higher magnification, this structure appears as a flattened cisterna. In immature erythroblasts this phenomenon appears as short stretches, while in most of the further differentiated erythroblasts a practically continuous line along the cell membrane is observed. The same abnormality is present in part of the erythrocytes in bone marrow and in peripheral blood. In these erythrocytes, however, only stretches of the membrane showed the abnormality (Figure 3). An artefact can be excluded since a similar picture was never observed in other identically treated bone marrow or peripheral blood samples. We suggest this structure is a supplementary double unit membrane inside the cell wall. Its origin could be either the result of an invagination of the cell membrane, comparable to what is observed in the Schwann cell or an accumulation of cytoplasmic membraneous structures (e.g. endoplasmic reticulum, Golgi apparatus, nuclear membrane). The possibility of a de novo originating 'new double membrane' should also be considered. Further observations will have to settle the exact nature

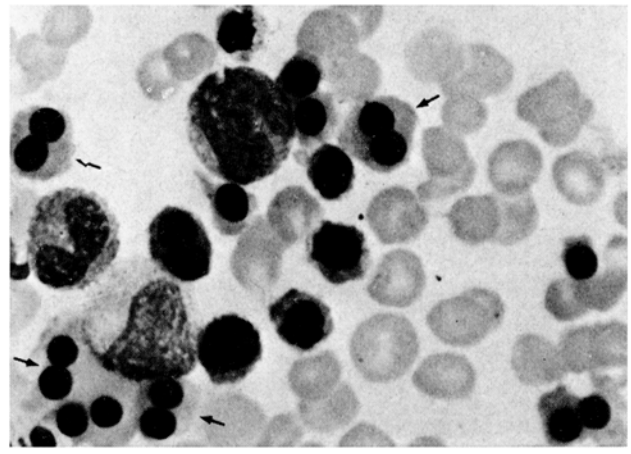

Fig. 1. Bone marrow sample from Hempas patient showing numerous binucleated erythroblasts (May Grunwald Giemsa stain).

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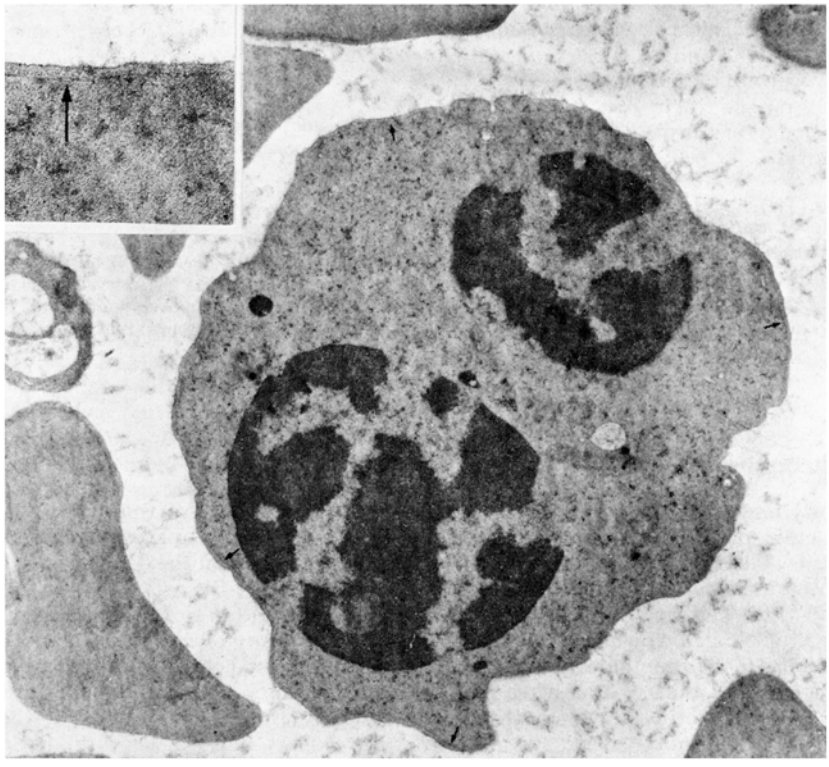

Fig. 2. Electron microscopic picture of a binucleate erythroblast with the described membrane anomaly. × 12.000. Inset: a higher magnification of the double unit membrane. × 36.000.

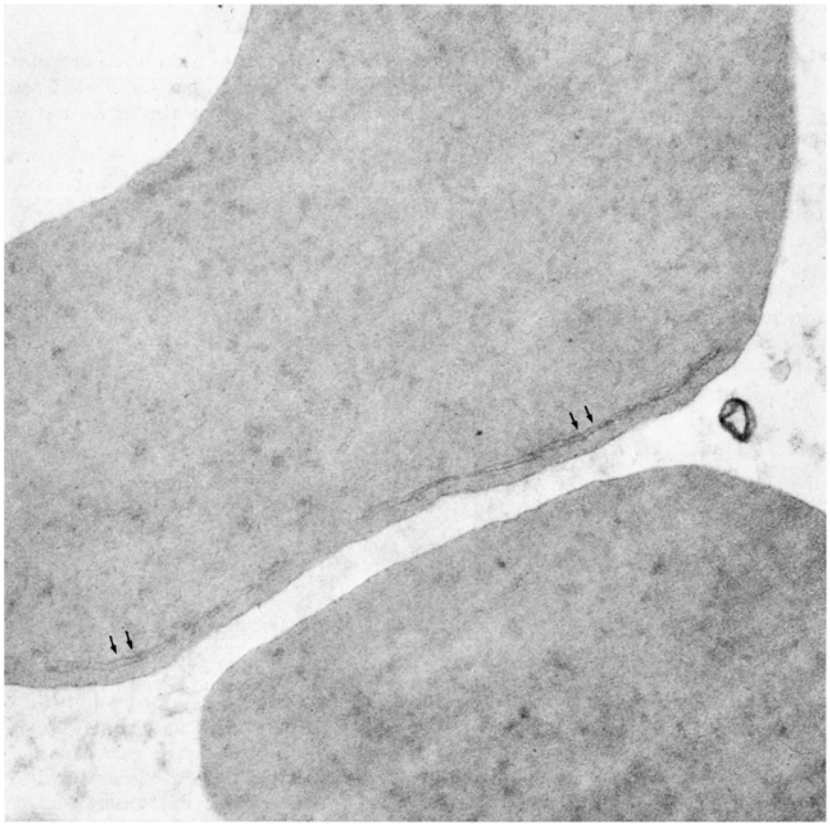

Fig. 3. Electron microscopic picture of an erythrocyte demonstrating stretches of the described anomaly. × 36.000.

of this structure. Abnormalities of the Hempas erythroblasts have recently been mentioned by HEIMPEL et al.[6] and by WONG et al.[7].

We suggest that the cell membrane anomaly, when it extends to a large part of the periphery in a late erythroblast, impedes postmitotic cell division or enucleation, this enucleation being a process similar to a cell division without a previous nuclear division[8]. This anomaly thus results in an intramedullar accumulation of the most affected erythroblasts and in ineffective erythropoiesis. The less affected erythroblasts can still pursue their maturation and appear in the peripheral blood as erythrocytes with stretches of the same abnormality.

Résumé. Description d'une anomalie de la membrane cellulaire des érythroblastes et des érythrocytes chez les malades atteints de «Congenital Dyserythropoietic Anaemia, type II». Les auteurs suggèrent que cette anomalie interfère avec la division cellulaire et est la cause de la binucléarité et de l'érythropoièse inefficiente rencontrées dans ce syndrome.

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[6] H. HEIMPEL, J. FORTEZA-VILA and W. QUEISSER, Scientific Exhibition at the XIIIth International Congress of Haematology (Munich 1970), p. 391.

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[8] E. SKUTELSKY and D. DANON, Expl. Cell Res. *60*, 427 (1970).

[9] We thank Prof. V.J. DESMET for the use of the electron microscope, Dr. H. VERHAEGEN for his help in the investigation of the patient under his care and Miss A. PINNOY for her skilful assistance.

The Kidney and Utilization of Erythropoietin

The metabolism of erythropoietin is poorly understood. Several studies have shown that the liver is probably implicated in the catabolism of the hormone[1,2] and utilization by the erythroïd marrow has also been incriminated[3]. However we have shown recently that neither hypoplasia nor hyperplasia of the erythroïd marrow modify the disappearance rate of erythropoietin in the rat[4]. On the other hand, it has been demonstrated that renal tissue or extracts are able to destroy erythropoietin in vitro[5,6]. This effect could be non-specific and not indicative of a physiological function of this organ. In order to precise this point, we have compared the effects of nephrectomy and ureteral ligation on the disappearance rate of exogenous erythropoietin in the rat.

Male Wistar rats, weighing from 180 to 200 g, have been submitted to bilateral nephrectomy or to ligation of both ureters. 48 h after nephrectomy and immediately after or 48 h after ligation of the ureters, 2 ml of plasma with high erythropoietic activity from hypoxic rats of the same strain (containing 2 to 4 units of erythropoietin