EDITORIAL

The Discocyte-Stomatocyte Equilibrium of Normal and Pathologic Red Cells

By R. I. Weed and M. Bessis

The DISCOCYTE-ECHINOCYTE transformation has become well known through the studies of Jolly, Ponder, Teitel-Bernard, Furchgott and Ponder, and, more recently, by Weed et al. and Bessis and Lessin. This subject has been recently reviewed in this journal by Brecher and Bessis. Certain characteristics of this transformation have been established. Intrinsic factors (i.e., depletion of ATP or extrinsic agents (e.g., lysolecithin, anionic detergent-like compounds, uranyl salts, sodium oleate, or elevated pH) can induce normal discoid erythrocytes to undergo the echinocyte transformation. This transformation also appears to be dependent on intramembrane calcium and its turnover. Exaggeration of the predisposing conditions, such as by employing increased concentrations of extrinsic agents, will lead to the formation of spheroechinocytes and prelytic spheres that are not reversible.

Pathologic erythrocytes, no matter what their shape, (e.g., poikilocytes, acanthocytes, or sickle cells) can, like normal red cells, respond to these same agents and develop echinocytic forms. The underlying pathologic shape persists, and secondary (new) spicules may be superimposed on primary spicules so as to give rise to echinopoikilocytes (e.g., echino-sickle cells, echinoacanthocytes, etc.).

In spite of the number of studies dealing with the distinctions between echinocytes, on one hand, and various other types of crenated or spiculated cells (such as acanthocytes, spur cells, burr cells, keratocytes, etc.) on the other, it is apparent that confusion persists in the literature in regard to these forms.

Even less well known and appreciated than the discocyte-echinocyte equilibrium is another type of shape change. This is the discocyte-stomatocyte transformation, which, in a sense, is the converse of the echinocytic transformation. The limited number of investigators who have studied the stomatocytic change have described this transformation as occurring with decreased pH as well as with certain chemical agents, particularly cationic detergent-like compounds and nonpenetrating anions. Low concen...
trations of these agents produce cup-shaped erythrocytes (Fig. 1) that, for convenience, we call stomatocytes, since on a smear the cells appear as if they have a mouth. As with the echinocytic agents, increased concentrations of the stomatocytic agents lead to the production of sphero-stomatocytes and finally prelytic spheres (Fig. 2A) that are not reversible.\textsuperscript{17}

Although sphero-stomatocytes and sphero-echinocytes may resemble one another with the optical microscope, they have different and distinct origins that can be appreciated with the scanning electron microscope, even in the end stage spherical forms (Fig. 2A and B). Thus, it now appears necessary to revise somewhat the scheme proposed by Deuticke\textsuperscript{12} that suggested that both echinocytic and stomatocytic factors give rise to the same spherocyte. Certain other modifications of Deuticke’s scheme seem justified. He suggested that

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**Fig. 1.** Stomatocytes produced by chemical agents. (A) $7.5 \times 10^{-6} \text{M}$ chlorpromazine (Hct 1%); (B) $1 \times 10^{-6} \text{M}$ chlorpromazine (Hct 1%).

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**Fig. 2.** Appearance of a sphero-stomatocyte and a sphero-echinocyte. (A) Sphero-stomatocyte produced by $1.5 \times 10^{-6} \text{M}$ chlorpromazine (Hct 1%). Note irregular area on left that represents remnants of the concavity. (B) Echinosphere produced by Na oleate, $2.5 \times 10^{-4} \text{M}$ (Hct 1%). Note the few remaining spicules.
echinocytic and stomatocytic substances are antagonistic, since a mixture of low concentration of the two types of agents may give a disk. Nevertheless, it is clear that these agents do not act on the same site, since both types of shape change can be superimposed on one another. Thus, under certain conditions, it is possible to have stomato-echinocytes, i.e., cells that are both crenated and have a cup shape.

Furthermore, it is of interest to note that like the echinocytic transformation, the discocyte-stomatocyte transformation can also be superimposed on underlying pathology of the cell. For example, deoxygenation of sickle cells previously rendered stomatocytic will result in the production of sickle-stomatocyte (Fig. 3). In this case, it appears that the polymerized rods of hemoglobin follow the general form that the membrane had at the moment of sickling. The cells deform somewhat, but they generally retain their cup-shaped appearance.

Of even more interest is the stomato-acanthocyte. When acanthocytes are

Fig. 3. Sickle-stomatocytes. After initial treatment with chlorpromazine, these cells were treated with sodium metabisulfite. Note sickle conformation superimposed on basic cut shape.
treated with stomatocytic agents, they develop a central concavity that increases in size as the concentration of the agent is increased. As further stomatocytic change is progressively superimposed on the acanthocyte, the spicules of the latter tend to disappear until the cell is completely transformed into a cup-shaped form (Fig. 4). Since this cup-shaped acanthocyte may resemble a discocyte under the optical (phase) microscope, it is possible that the "interconversion of acanthocytes and normal erythrocytes" produced by detergents (Tween 80)\textsuperscript{18} may, in fact, have represented the production of tomato-acanthocytes, interpreted as normal erythrocytes especially since Tween 80 is a cationic detergent agent.\textsuperscript{18}

It has not been our intent in this editorial to discuss the controversies regarding the mechanisms that underlie these curious changes in red cell shape produced by manipulation of the extracellular environment, but rather to demonstrate that, in addition to the discocyte-echinocyte transformation, there exists a very different discocyte-stomatocyte transformation that may also ultimately lead to the production of a spherocytic cell. We also wish to

Fig. 4. Stomato-acanthocytes. Cells from a patient with familiar acanthocytosis were treated with chlorpromazine. In lower left, note that all spicules except one appear to have been effaced by development of the stomatocytic form.
emphasize that the stomatocytic change, like the echinocytic change, can take place in pathologic cells and can be superimposed on the underlying structural pathology of the cells. These forms can be precisely evaluated with the scanning electron microscope. Once aware of their existence, they can also be appreciated quite easily in living cells and can be examined with a phase microscope or even on a blood smear, if one is cognizant of all the possible artifacts.

REFERENCES

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