Deformation of Red Blood Cells in Capillaries

Abstract. *The shapes of red blood cells in capillary blood vessels are reinterpreted from observations of human red cells. The parachute or umbrella shape often observed is not an axisymmetric shape as formerly assumed, but is the basic biconcave disk shape of the red cell with the upstream end flattened by the pressure gradient.*

The shapes of red blood cells in capillary vessels have been observed, and studies of the flow properties of red cell suspensions have led to the generally accepted view that red cells are highly deformable (*1*) and are regularly deformed in flowing blood (*2, 3*). However, the precise shapes which are assumed in flowing blood have not been analyzed in detail. We have reviewed the shapes of red cells in man and reinterpreted our results in light of current knowledge about the cell membrane, the cell contents, and the stresses acting on a particle in a viscous flow. We find that the parachute-like or umbrella-like shape often observed has been misinterpreted and that deformations are less radical modifications of the basic biconcave disk shape of the red cell than might be supposed (*4, 5*). The central notion of all earlier investigations is that, since the red cell membrane is quite flexible and the cell contents are fluid, it is relatively easy to produce an internal displacement of the cell contents which accounts for the main changes of shape observed as opposed to gross bulging or folding of the cell itself.

We have studied primarily vessels of the same order of diameter as red blood cells (that is, below 10 μ), but many of the effects also pertain to larger vessels. Our results are important to any analysis of blood flow in capillary vessels and to exchange across the capillary walls, since any such theory must be based on qualitative assumptions of the shapes involved. At least two analyses (*6, 7*) are based on erroneous suppositions of a paraboloid or parachute-like shape, which is a misinterpretation of the appearance of red blood cells in the light microscope.

Typical photomicrograms have been taken in man by means of the arm-chamber technique of Brånemark (*2*). The hamster cheek pouch, the rabbit ear, the mesentery, and many other tissues have also been observed; all give very similar results. In vessels approximately 7 μ and 4 μ in diameter (Figs. 1 and 2, respectively) the commonest shape (*4*) is an apparent parachute or jellyfish-like form. In vessels of smaller diameter a torpedo-like shape which may have tail flaps also occurs. This appears to be the parachute shape compressed and elongated. Although the general outline of a typical cell might be described as a parachute shape, the faint rear end is usually not straight, but curved (Fig. 1). Our interpretation is that the cells are still disk-shaped but with the rear end flattened and the front part thickened and bulged.

Synchronized flash techniques with exposures of 100 μsec at 0.06-second intervals give a high degree of resolution and permit following of a particular cell as it deforms. Large deformations and recovery can occur in very short times (of the order of 0.06 second), particularly at branchings of blood vessels and at tapered sections. Individual cells also deform rapidly during starting and stopping of flow which occurs normally in many capillaries.

Cells may change rapidly from a symmetric form resembling a biconcave disk to the parachute-like shape without large changes in the overall length or the shape of the forward end of the cell during acceleration from rest. It appears that there is no rotation from the rest position, in which the plane of the red cell disk is parallel to the axis of the capillary, to an axially symmetric one, which would be required in order to get the axisymmetric parachute shape usually implied from photomicrographs, such as Figs. 1 and 2.

A schematic interpretation of the distortion of the red cell is shown in Fig. 3. At rest, the cell assumes a disk shape and is only slightly distorted in order to fit into the capillary. During flow, the rear end blunts, and the front end begins to thicken slightly (Fig. 3b). In the parachute shape, the flattened rear portion of the cell becomes squeezed

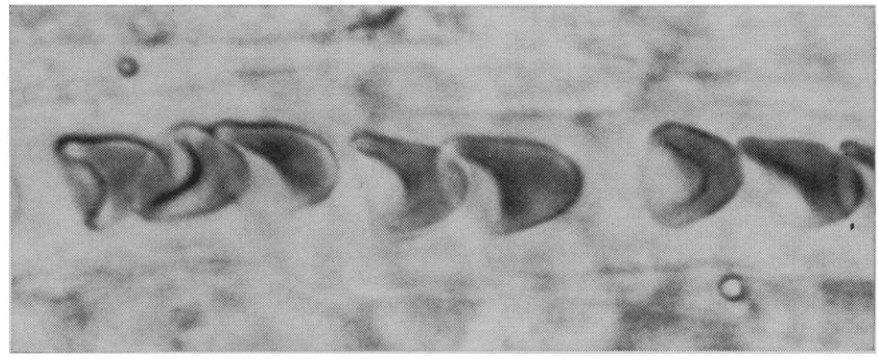

Fig. 1 Shapes of red blood cells in vivo in a capillary of about 7-μ diameter. Most of the cells show the parachute-like shape; the cell on the left shows in addition the tail-flap appearance.

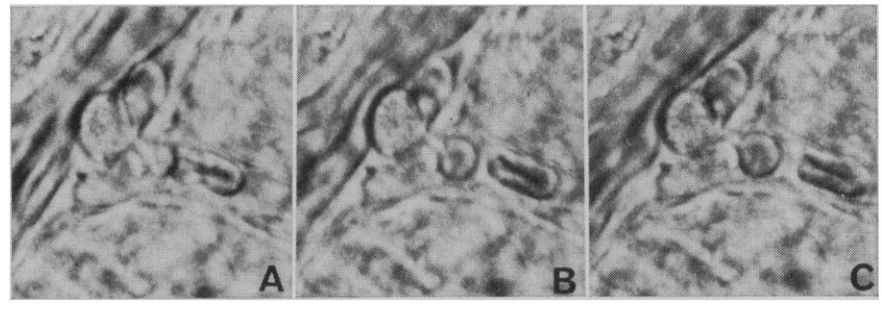

Fig. 2. Shapes of human red blood cells in vivo in a capillary of about 4-μ diameter. Sequence of black and white reproductions from successive frames of 16-mm color cinefilm. (A) Red cell squeezing into a narrow capillary. (B) Complete but distorted ring around the edge of the cell. (C) Structure similar to that in (B) except for the rear end which appears to have a gap in the ring. This results in a characteristic U-shape or hollow torpedo appearance.

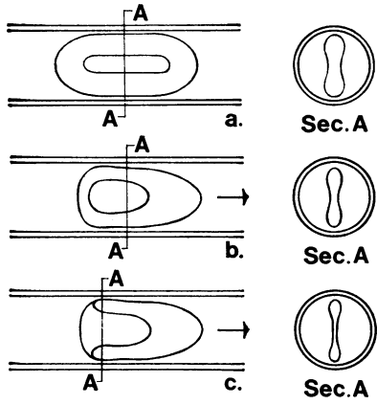

Fig. 3. Scheme of red cell deformation in a capillary of 7-μ diameter.

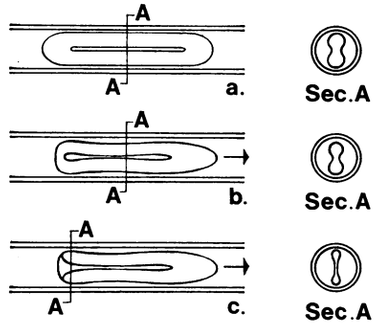

Fig. 4. Scheme of red cell deformation in a capillary of 4-μ diameter.

free of cell contents (primarily hemoglobin), which are now contained in the bulging front end of the cell. The displacement of the cell membrane, however, is relatively minor, and its form is essentially a disk squeezed flat at the rear of the cell. This deformation can be readily understood from consideration of the stresses acting on a cell. During any blood flow, there must always be a pressure gradient; that is, a pressure drop in the direction of flow. The higher pressure in the rear tends to compress the rear portion of the cell. During motion at a steady velocity, the configuration of the cell often remains relatively constant so that the cell contents are at rest with respect to the cell membrane and therefore are at constant internal pressure. The resultant force on the cell due to the differences of pressure at the front and rear outside of the cell is balanced primarily by shear stresses exerted on the membrane by the flow at the section where the bulging of the cell results in the least distance between the cell and the capillary wall. For uniform motion the net force on the cell must be zero. These qualitative ideas of pressure decrease and stress distribution have been substantiated by physical models (*8*) as well as by analytical solutions of idealized cases (*9*).

In a capillary about 4 μ in diameter, a cell at rest appears as a flattened ring, and the central concavity shows as a thin line running along the axis of the vessel (Fig. 4a). Driving pressure at the rear of the cell causes a local deformation with a typical flap or tail appearance often observed as a variation of the parachute-like shapes (Fig. 4b). As the cell contents are squeezed from the rear part of the cell membrane, the parachute-like shape is produced (Fig. 4c).

The size of vessel shown in Figs. 2 and 4 is close to the minimum diameter through which a red cell can easily pass. Gregersen has directly measured the minimum diameter in a polycarbonate filter (*1*) and gives a value of 2.4 μ for the passing of 70 percent of red cells. Based on a study of the size, area, and volume populations of normal human red cells Canham and Burton (*10*) predicted the minimum cylindrical diameter to be 3.72 μ. These studies and previous information on sphering and hemolysis of red cells have suggested that the area of a red cell cannot be increased more than a few percent without hemolysis of the cell. The deformations proposed above are possible within the restriction of constant volume and surface area of the red cell. However, if the parachute and torpedo shapes shown in Figs. 3c and 4c were interpreted as axisymmetric surfaces, the area of the cell membrane required would be greater than that which would produce hemolysis. In the vocabulary suggested by Fung (*11*), the deformations proposed are isochoric and nearly applicable, whereas axisymmetric or paraboloid shapes would require considerable stretching of the cell membrane. The deformations proposed require that the membrane be quite flexible in bending. That this is so is quite commonly accepted and supported, for example, by estimates by Fung (*11, 12*), based on the normal shape and the sphering process.

The shapes described above occur also in blood vessels with diameters of 10 to 20 μ (Fig. 5). Figure 5 suggests that the apparent interlocking of the parachute shapes as, for example, in Fig. 1 is actually an overlapping of the distorted disk shapes. The overlapping and inclination of the cells may result in the illusion that the wide end of the parachute shape is open, whereas it actually has cell membrane stretched across it. In still larger blood vessels (40 μ) the shapes of red cells have been observed by Monro (*13*), and blunting of the rear end and bulging of the front end occurs there also.

The shapes proposed here are not considered to serve any physiologic purpose other than the transport of the red cell through the capillary. It has been suggested that because of its increased surface area the paraboloid shape should be more effective in facilitating gas exchange (*6*). The shapes described here would give effectively a lower ratio of area to volume. This is not thought to be physiologically significant, because the diffusion occurs very rapidly and easily across the dimensions of the order considered here. Canham and Burton (*10*) have suggested that the basis for removal of old red blood cells by the spleen may be mechanical and controlled by the minimum cylindrical diameter through which the cell can pass. The shapes in vessels larger than this minimum diameter are the

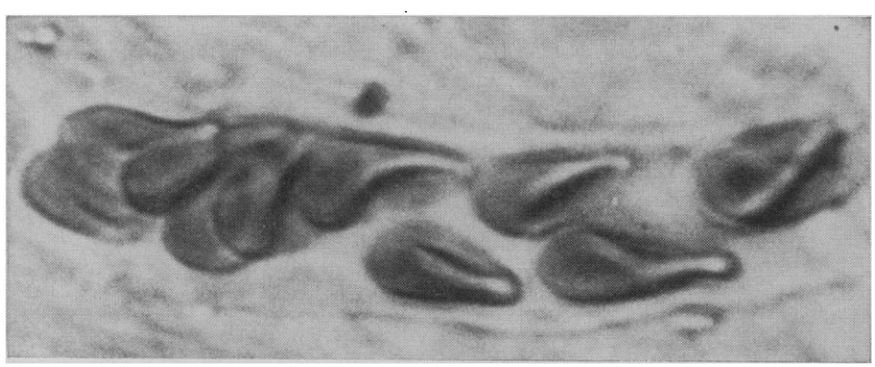

Fig. 5. Red blood cells (human) in vivo in a vessel of about 12-μ diameter.

result of the reserve of flexibility which the red cells have in these larger vessels rather than of functional physiological significance.

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Brain Lesions, Obesity, and Other Disturbances in Mice Treated with Monosodium Glutamate

Abstract. *In newborn mice subcutaneous injections of monosodium glutamate induced acute neuronal necrosis in several regions of developing brain including the hypothalamus. As adults, treated animals showed stunted skeletal development, marked obesity, and female sterility. Pathological changes were also found in several organs associated with endocrine function. Studies of food consumption failed to demonstrate hyperphagia to explain the obesity. It is postulated that the adult syndrome represents a multifaceted neuroendocrine disturbance arising from the disruption of developing neural centers concerned in the mediation of endocrine function.*

Parenterally administered monosodium glutamate (MSG) produces an acute degenerative lesion in the inner retina of normal neonatal mice (*1*). Although the acute lesion has been described both light and electron microscopically (*2*) and several biochemical parameters have been studied (*3*), the specific mechanisms underlying the effect of MSG on retinal neurons have not been definitively clarified. That MSG treatment might have a similar deleterious effect on neurons in other regions of the central nervous system (CNS) has apparently not been considered. A suspicion that hypothalamic lesions might be associated with glutamate treatment was aroused by the observation that several months after neonatal mice were treated with glutamate, for purposes of inducing retinal pathology (*4*), they became quite obese. Data establishing that glutamate treatment does induce brain lesions are now presented, and a preliminary characterization is given of a syndrome resulting from glutamate treatment which features obesity as its most striking characteristic.

Ten litters of Swiss albino mice, 2 to 9 days old, were killed from 1 to 48 hours after a single subcutaneous injection of MSG (dosages varied from 0.5 to 4 mg/g), and brains were examined by light microscopy for acute pathology. Brain lesions characterized by intracellular edema and neuronal necrosis developed within a few hours of treatment at every dose tested, including 0.5 mg/g (Fig. 1a). Certain structures located in a paramedian plane and bordering on the roof and floor of the third ventricle were preferentially affected. At the base of the brain, preoptic and arcuate nuclei of the hypothalamus were selectively destroyed along with scattered neurons within the median eminence (nuclei tuberales). No acute changes were found in other hypothalamic areas or in the pituitary. Dorsally, the subcommissural and subfornical organs and neuronal groups contiguous with them were involved, including the medial habenular nuclei and neurons of the rostral hippocampus (dentate gyrus). Acute lesions were also found in brains of adult mice given high doses (5 to 7 mg/g) of MSG subcutaneously (Fig. 1b). Whether lower dosages than those tested might induce neuronal pathology in either the immature or mature CNS requires further systematic investigation. Brain lesions were also found in the C57BL/6 strain of mice and in albino rats after MSG treatment in the neonatal period.

To study the possibility of long-range effects accruing from glutamate treatment of the neonate I followed five litters of Swiss albino mice, consisting of 38 healthy animals, from birth to 9 months of age. Twenty animals received subcutaneous injections of MSG daily from 1 to 10 days after birth, according to a dose schedule described by Cohen (*4*); 18 controls received no treatment. All animals were weighed individually on a weekly

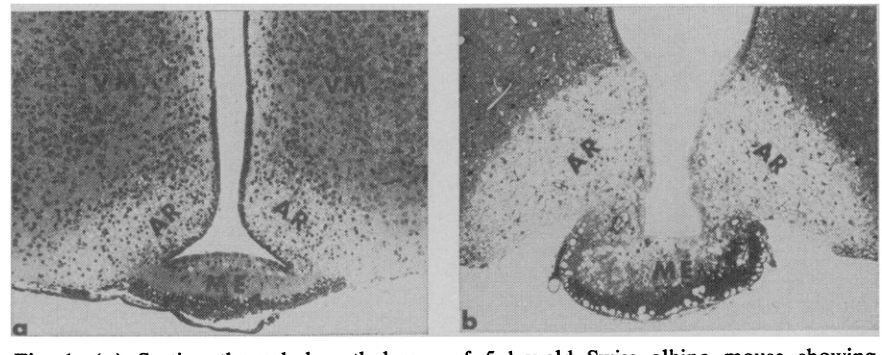

Fig. 1. (a) Section through hypothalamus of 5-day-old Swiss albino mouse showing lesion formation 3 hours after a subcutaneous dose of MSG (1 mg/g). Scattered neurons in the median eminence (*ME*) are necrotic with bloated cytoplasm and pyknotic nuclei. The majority of neurons in the arcuate nuclei (*AR*) are necrotic, but those of the ventromedial nuclei (*VM*) are unaffected (× 100). (b) Section through hypothalamus of adult C57BL/6 mouse 3 hours after a subcutaneous dose of MSG (6 mg/g). The arcuate nuclei (*AR*) are completely destroyed along with neuronal constituents in the median eminence (*ME*). Capillary lumina are empty and widely dilated because this animal was killed by perfusion of glutaraldehyde through the ascending aorta (× 115).