

MATHEMATICAL MODELS AND ENIGMAS IN EVOLUTION OF ERYTHROCYTES

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Abstract:-- The mammalian erythrocyte after extruding primitive marginal bands and nucleus, attains a kiting biconcave form with high surface/ volume and low inertia, deforms readily to enter tight confines, regains its form even though the endoplasm is purely viscous, by means of tensile elasticity of the cytoskeleton and probably by pressure and tension.

Key Words:-- Biomathematics and evolution of erythrocytes

1. Introduction

The mammalian red blood cell has a biconcave, disk-like shape and lacks a nucleus and associated organelles. Early phylogenetic studies on erythrocytes (see Scott, 1966) were provocative but problematic. How did the unique mammalian characters arise? The fossil record reveals no record of soft organ structures, or blood cells. This imperfect record was always enigmatic, failing to reveal clear transition (especially physiological). Amphibians and reptiles that exist today, as well as the lungfishes and modern birds, are disparate branches of the phylogenetic tree. The best evidence available is ontogenetic (i.e., erythropoiesis), but ontogeny is not always predictable of a phylogeny. A biomathematical analysis of hematological structures explains evolution up to mammalian grade and some paradoxes of cell structure and function.

2. Problem Formulation

Physical and mathematical analyses are defined when possible. Several new hypotheses are presented. Some definitions are:

t_n = total number of triangles in ring n .

e_n = total edges forming triangles in ring n .

$T_n = t_1 + \dots + t_n$ = total triangles in Hexagon n .

$E_n = e_1 + \dots + e_n$ = total edges within Hexagon n .

s_n = total number of squares in ring n .

d_n = total edges forming squares in n .

$S_n = s_1 + \dots + s_n$ = total squares within Square n .

$D_n = d_1 + \dots + d_n$ = edges for squares in Square n .

3. Problem Solution

3.1. Ontogeny. Ontogenetic evidence, the best available, predicts evolution from erythropoiesis of mammals and non-mammalian vertebrates. Erythroblasts develop to reticulocytes and finally mature as erythrocytes that enter the blood circulation. Non-mammal cells become "biscuit-shaped ellipsoids", rather flattened, swollen centrally by the presence of an internal discrete (i.e., relatively solid) nucleus fixed

in place by supporting ties of vimentin. Other organelles such as mitochondria are present during the time that ATP energy is turned toward the production of hemoglobin molecules (Hb) for gas transport. Marginal bands (tubulin) encircle the erythrocytes.

The spherical "erythroblast" becomes an ellipsoidal erythrocyte in non-mammals, shaped to squeeze through apertures invading the early-forming or established blood circulation. The cell becomes almost bilateral, indicative of forward or backward movement. These cells move through large blood vessels in flowing blood plasma, and eventually through capillaries sometimes thinner than the diameter of the erythrocyte. Erythrocytes are flexible, containing oxyhemoglobin or hemoglobin, and bend from strains (Bull and Breton-Gorius, 1995).

In mammalian cells, the nucleus and other organelles are "extruded" after Hb production ends. Occasionally in other vertebrates, rarely in invertebrates (Scott, 1966), and especially in some poorly respiring salamanders, the nucleus is extruded. In mammals the anucleate cell is the "definitive" mature erythrocyte in circulation. The erythrocyte completes underpinning the phospholipid membrane with a spectrin cytoskeleton (Palek, 1995, and others).

The nucleated erythrocyte gave rise to the biconcave anucleate disk, and is illustrated by the ontogeny of primitive mammals such as marsupials (Cohen et al., 1990). The yolk sac "primitive" blood cells were larger, nucleated, elliptical but discoid, and thickened centrally by the nuclear bulge. There was a marginal band and a surface spectrin network. Three days later over 90% of the cells in the circulation were anucleate definitive erythrocytes. The anucleate amphibian *Batrachoseps* had erythrocytes similar to those of the marsupial "neonates". In "primitive" yolk sac erythroblasts of several mammals, the ontogenetic appearance of marginal bands was discovered (Van Deurs and Behnke, 1973).

Hemoglobin differs in adults from that in yolk sac “primitives”, but mouse primitives eventually produce adult Hb. There are at least two normal adult and several embryonic hemoglobins (e.g., Brotherton et al., 1979).

In mammals, the abortion of the nucleus occurs in the reticulocyte. The remaining cell membrane (with cytoskeleton) contains endoplasm, hemoglobin (Hb) and a few enzymes. These “mature” erythrocytes (and a few reticulocytes) invade the circulatory system in great numbers (mostly from bone marrow). Enucleation is difficult to explain as adaptation. Apparently the nuclear loss diminishes the volume, increasing the surface to volume ratio. Enucleation helps make the cell biconcave. Another speculation suggests that a nucleus costs ATP energy and drains off HbO₂ for no useful purpose.

The sequence of loss of mitochondria, marginal bands, vimentin and nucleus, in that order, would suggest phylogeny. Enucleation is preceded by loss of the constraining marginal bands (= tubulin). Usually the human’s nucleus and filaments (= vimentin) are lost when traversing the wall of a marrow sinus, sometimes later and sometimes before, and this is caused by contortions of the cell. The nucleus envelops itself in membrane materials and some Hb and pulls away from the remainder of the cell. Mitochondria were reduced in size and number earlier (Bull and Breton-Gorius, 1995). Loss of the bands facilitates subsequent enucleation, but the advanced camel enucleates and keeps its bands, although camel cells assume an elliptical shape. Generally, the mammal erythrocyte becomes dimpled.

3.2. Motion. Erythrocytes have such a relatively low volume (hence little mass) that low inertia, related to their low Reynolds number, practically freezes them into the surrounding plasma. When the plasma flows fast, the biconcave mammalian red cells, some stacked in roulettes, are carried past.

Ellipsoids are not fusiform enough to eliminate a change in momentum from eddies. Either end can move forward in a current or tube. The ellipsoidal non-mammal cell, or camel cell, is streamlined enough to diminish friction from the current and capillary wall.

Alexander (1951: 36) showed that a streamlined body has only 0.05 to 0.1 of the drag on a sphere of equal volume (traveling at the same velocity in the same fluid). Or, the streamlined form could carry more volume moving with the same drag.

A disk form has even more drag than a sphere, hence the mammal’s biconcave disk is no adaptation

for streamline advantage. In consideration of Reynolds number for small cells, I note that the disk or sphere suffers the most drag. *Voila*, the disk-like mammal red cell can transform itself into a perfectly streamlined fluid-like projectile, even tapered behind, for entering tight places.

The small volumes tend to be constant even in twisted, deformed, and other prolated forms. Although not so prolated, the biconcave mammalian “sphere” [the biconcave shape would be a sphere if the opposing dimples were everted] keeps a surface appropriate for a sphere, but dimpling shows diminished volume. This results in a huge surface to volume ratio. There are two obvious advantages of the high ratios. The gas exchange function is enhanced, and the low inertia of low volume limits movement independent of the viscous plasma. The two fluid-like substances, cells and plasma, move as one. The biconcave shape is pushed along, no matter what its orientation in the flow.

3.3. Surface area. In all erythrocytes, the extremely thin, fluid-like cell membrane and the purely viscous endoplasm are constrained by a flexible, slightly contractile cytoskeleton comprised of tiny equilateral triangles of spectrin molecules. This geodesic form is not only porous, but has a fluidity of form, which geodesic structures can have. The microtubule bands circumscribe and augment the non-mammal’s spectrin cytoskeleton. Their absence in mammals permits the endoplasm and membrane to assume radial symmetry.

The cytoskeleton and membrane act as a lasting envelope resisting permanent invagination from strain forces, which the purely viscous endoplasm could not do, and in mammals prevent everting of the curved extensive surface within each dimple. Other factors combine to create or maintain the mammal’s biconcave form. (A) The porous framework allows strains to shape the viscous endoplasm, yet its limited elasticity can reform the biconcave shape rapidly. (B) Can this be effected in part by the phospholipid membrane? The entire membrane is comprised of tiny columns within a curved surface, and any differential created would seemingly reform as vertical columns standing together (Canham, 1970). (C) The fluid-like cell membrane is perhaps somewhat contractile physically as a fluid drop having cohesion inside and surface tension pulling the surface. (D) The bending energy is minimal for such a “giving” surface.

The biconcave shape of a visco-elastic spheroid may result from minimal bending energy expended (Canham, 1970; Korpman et al.1976, 1977), if the

material is two dimensionally isotropic on the surface, the material of the surface is easily deformed by tangential forces but resists even small forces of dilation, and the response to the ambient force increases with deformation.

The most feasible explanation for energy used is that a favorable surface to volume ratio of the red cell allows its surplus to reform the shape. Shear, a differential effect on the red cell by streams of fluid, is also friction from the surrounding blood vessel or impacts with other blood cells. The nature of whole blood when compared to other thick fluids, shows that shear deforms cells and causes loss of viscosity. The deformed cells become irregular ellipsoids. Strain, superficial tensile and bending strain, uses energy, a reaction against substances pushing against the cell.

Red cells are not like rubber bands; when a rubber band is stretched in the direction of tension it narrows the band; it also gets thinner. The red cell skeleton is only two molecules thick. It cannot get thinner. Compression across the width must equal extension. Mechanics seem uniform over the surface. Therefore, the cell surface must be altered in all directions simultaneously by applied tension.

If the shaping comes from bending resistance, the cell *must* have lost volume. This likely followed extrusion of internal organelles. In no way does this minimization explain why the cytoskeleton is evolved from triangles (i.e., hexagons), and why even primitive animals have spectrin triangles.

3.4. Geometry of triangles. For paving a surface with triangles arranged in hexagons, the well-known progression (below) allows one to determine the ratio of edges to the triangles, and to determine a rate of formation. Let $n = 1, 2, 3,$ to denote any “ring” of triangles. The value $n = 1$ corresponds to the first ring of triangles joined to form a regular hexagon (see Fig. 1). The value $n = 2$ corresponds to the second ring added outside the $n = 1$ ring. When $n = 1$, six triangles comprise 12 edges that form the first hexagon (hex 1). Secondly, add two triangles (using only three edges) at each of the outside vertices of hex 1. Up to this point,

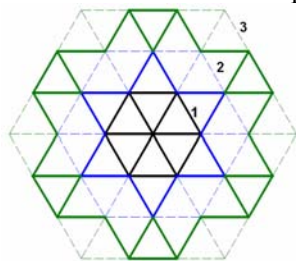


Figure 1. Rings of hexagons from triangles ($n = 1-3$).

the $n = 1$ ring contains six triangles and 12 edges, and the $n=2$ ring contains $6 + (6 \times 2) = 18$ triangles and $(6 \times 2) + (6 \times 3) = 30$ edges. The outside edges of the $N = 2$ ring form a larger hexagon (hex 2). When $n = 3$, add three triangles on each side of the hex 2, using only 5 edges, and add two triangles at each vertex of hex 2 using three edges. Therefore $t_3 = 6(3 + 2) = 30$ and $e_3 = 6(5 + 3) = 48$. For $n 1, 2, 3$

t_n	T_n	e_n	E_n	18	24	30	42
6	6	12	12	30	54	48	90

The values of t_n increase by 12 and of e_n increase by 18. The sequences of numbers t_1, t_2, \dots and e_1, e_2, \dots are each arithmetic sequences, and it follows for each $n \geq 1$ that T_n and E_n can be determined:

$$T_n = t_1 \dots + t_n = \sum_{k=1}^n tk = \sum_{k=1}^n 6(2k - 1)$$

$$= 6 [2 (\sum_{k=1}^n k) - \sum_{k=1}^n 1]$$

$$= 6 [2(n(n + 1)/ 2) - n] = 6 n^2$$

where $2(n(n + 1)/ 2) = (\sum_{k=1}^n k)$ is Gauss' standard

identity. Similarly, $E_n = 3n(3n + 1) = 9 n^2 + 3n$. Then, the ratio of edges to triangles obtained by $(e_n - e_{n-1}) / (t_n - t_{n-1}) = 3/2$ for $n > 1$, and it follows that

$$e_n / t_n = 6(3n - 1) / 6(2n - 1)$$

$$= 3/2 + 1/2(2n - 1)$$

$$E_n / T_n = 3n(3n + 1) / 6 n^2 = 3/2 + 1/2n$$

for $n \geq 1$. Either of the ratios is approximately 1.5 when n is large. Similarly, we find the ratio of edges to squares and larger squares to their component tiny squares (see definitions above) as follows:

$$s_n = 4(2n - 1) \text{ and } d_n = 4(4n - 1)$$

$$S_n = 4n^2 \text{ and } D_n = 4n(2n + 1) = 8n^2 + 4n$$

$$(d_n - d_{n-1}) / (s_n - s_{n-1}) = 2$$

$$d_n / s_n = 2 + 1 / (2n - 1)$$

$$\text{and } D_n / S_n = 2 + 1/n.$$

Therefore, $E_n / \text{area of Hexagon } n = 2\sqrt{3}$ as $n \rightarrow \infty$ and $D_n / \text{area of Square } n = 2 + 1/n$ as $n \rightarrow \infty$.

The ratio of $D_n / S_n = 2 + 1/n \rightarrow 2$ as $n \rightarrow \infty$. The total number of edges is double the number of tiny squares. $E_n / T_n = 3/2 + 1/2n \rightarrow 3/2$ as $n \rightarrow \infty$.

The number of spectrin edges in triangles greatly outnumber those of hypothetical squares,

$$T_n / S_n = 6n^2 / 4 n^2 = 1.5.$$

Note that the area of an equilateral triangle with side length one is $\sqrt{3} / 4$ and a tiny square with side one has an area of one. The number of edges of triangles per unit of enclosed area when forming hexagons has a

limit ≈ 3.46 , while the number of squares has a limit of 2. For this reason, no economy of spectrin is gained by use of triangles, but the polygons are smaller, and of course more stable than a small square.

In geodesic construction (of domes and spheroids) a basic rule states that triangles provide stability, and cubic patterns are unstable. It is said, "tie a diagonal strut across each small square". A curved surface may be formed of flat polygons, if they are great in number and tiny enough to fit together. Triangle construction with smaller polygons allows the cytoskeleton to better conform to the inner curvaceous surface of the membrane (in all the vertebrates), and in the living cell allows bending and provides tensile strength in all directions against any strains during the cell's travels. The biconcave cytoskeleton has an even freer flux allowing deformability.

A sphere can not bend nor invaginate without expanding the surface and changing shape or volume. The fluid-like non-mammal cell does bend, and also deforms, even with the handicap of a central nucleus. The mammal's biconcave disk is more adaptable in kiting in the blood flow or in "oozing" through tight places. It assumes shapes in capillaries called parachutes, bullets and slippers (Fung, 1981).

3.5. Curvature, triangles, spectrin. The problem with elaboration of a polygonal structure onto or underpinning an inner curved surface of a spheroid is somewhat analogous to creating a "3-frequency" geodesic hemisphere (or spheroid) with equilateral triangles of sheet metal covering a wooden framework (Cartwright, 1974). A coefficient of curvature for the chord factor is 0.4124, and an edge of the equilateral triangle has height of the triangle/ $\sin 60^\circ$. The radius r of the framework is, $r = \text{edge length} / 0.4214$.

The noodle-like, equal-sized lengths of spectrins in the polygons of the cytoskeleton of vertebrate red cells are comprised of homologous triple-helical segments, so that an alpha spectrin lies besides a beta spectrin, and the ends meet either at an actin anchor post, or "head to head" with another pair of spectrin chains. Thus, each edge of the triangle is made up of alpha and beta chains linked with other alpha and beta chains at a dimer interaction midway between the actin corners of a triangle. Since the skeleton is "laminated" onto the undersurface of the fluid-like phospholipid cell membrane, the protein lengths seem to be the source of what tensile strength there is at any edge of any triangle (i.e., of hexagons or pentagons). The actin posts seem to anchor the ends of the spectrin segments, although one might presume that the

spectrin length spaces the network or lattice at functionally important set distances between patterned actin connections. In any case, the skeleton maintains structural integrity and even a limited elasticity when the membrane and contents are experimentally removed by hemolysis, leaving a "ghost skeleton".

Another way to "measure" the edge is by the arrangement of amino acids. Spectrin consists of two chains composed of homologous 106-amino acid repetitive segments, with alpha having 20 segments and 2 non-homologous ones, and Beta having 17 homologous segments and termini binding sites. The two chains associate with two other chains midway between the two corners of the triangle. There are other ankyrin binding sites, one in the 15th segment, and another where spectrin binds with actin and the 4.1 protein. Thus, tetramers form the struts (alpha-beta+alpha-beta).

The development of the mesh network will allow the cytoskeleton, once it is formed, to help maintain the curvaceous shape of the overlying membrane, as if it were nailed to a plastic tarp. In the mammal cell with its inflection (latitudes) circling all around the dimple on either surface of the cell, the construction by small triangles project tensile vectors radiating in various directions, allowing the spheroid structure to deform. The triangles cannot stretch much. Neither can the plate-like hexagons stretch or contract. Bulging of the endoplasm or invagination is not constrained much by the tiny polygons, because there is so much surface for so little volume. The inner contents can move about, and even the dimple on the surface can move as a wavelike ripple of the surface. Dimpling of equal sized hexagons was demonstrated by Bull with his polyethylene model. In a normal erythrocyte, or in the crude model, the hexagons cannot evert, the cytosol cannot expand upward or into the dimpled center, and the cytoskeletal structure absorbs forces uniformly.

3.6. Equations for Biconcave Shape. Fung (1981) reviews early equations. The Cassini equation consists of all points (x,y) for which the product of the distances between (x,y) to both of the foci (o) equals b^2 .

$$[(x - a)^2 + y^2] [(x + a)^2 + y^2] = b^4$$

This describes a circle with radius b and center at $(0,0)$. If a and b are constants, two foci are in the xy plane located at $(-a, 0)$ and $(a, 0)$. A Cassini oval that resembles the profile of a mammalian red blood cell is shown in Fig. (2), and for this particular shape, arbitrary values are $a = 1$, $b = 1.1$. Shown within is a right triangle showing b and a , and a distance to the periphery at $b(2^{1/2})$. The distance a is the distance

from a focus to the center of the oval. To determine the volume and surface area of a form shaped like a mammalian red blood cell we obtain a solid of revolution with volume V and surface area (S).

$$V = 2 \int_0^{\sqrt{a^2+b^2}} 2\pi x [(\sqrt{b^4 + 4a^2x^2}) - (x^2 + a^2)]^{1/2} dx$$

The integral is well known to be very difficult, but by standard algorithms the approximate value for our specified values of a and b provide the value for V , which for the oval above ≈ 6.789 units cubed. The integral for surface area is also complex, as follows:

$$S = \int_0^{\sqrt{a^2+b^2}} 2\pi x b^2 [b^4 - a^4 + 3a^2x^2 + x^2 \sqrt{(b^4 + 4a^2x^2)/b^4 - (x^2 - a^2)(b^4 + 4a^2x^2)}]^{1/2} dx$$

Similarly we obtain for the spheroid above a value for $S \approx 19.854$ units squared. This agrees with observations, but our Volume is considerably lower.

I emphasize that by the study of the Cassini ovals, the biconcave shape obtained is not to be considered so much the path of a moving point on an ellipsoid, but instead an evolutionary consequence of adjusting the product of two variables. These are the distance from the center of the biconcave disk to a focal point on x at a , and the distance from that same focal point to the lowest point on the dimple of the upper side of the biconcave disk [or on the underside dimple].

If one reduces the inner volume, either the value a diminishes or the value along y diminishes. To maximize the surface area of the biconcave disk, or the periphery of the Cassini oval, the reduced volume requires a dimpling, usually a double dimpling. Or it could be resolved by prolation to an elongate ellipsoid.

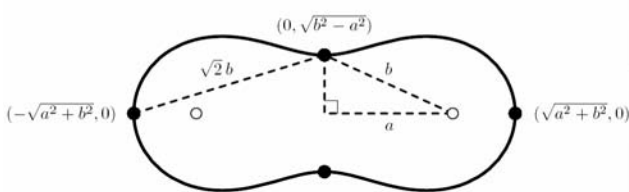


Figure 2. Cassini Oval. See text

Cassini ovals reportedly have “empirical” values.. Indeed they have more utility. Long (2004), who suggested the mammal cell was some kind of prolate form like a sphere (with poles inverted as “dimples”), might have added that the mammal form became radial by loss of the marginal bands. Then volume and therefore mass were diminished by loss of the central nucleus. The dimpled spheroid bulges up and away from the two axes, or down and away for the lower

quadrants. This may be clarified perhaps by the Pythagorean Theorem, by examining the right triangle shown in the oval above, and constructing a square on each of the three sides. Inspecting only the right upper quadrant, i.e., the upper right triangle, the square on the hypotenuse (b) is huge upward and to the right, whereas either of the other squares is smaller. The important thing is, one obtains an increasingly huge bulging effect by shortening the minor axis. This observation becomes interesting in regard to consideration of intracellular pressure.

3.7. Surface and Pressure. Intracellular pressure of mammalian red blood cells needs study. Based on consideration of the undersurface of the red cell membrane, I hypothesize there is a pressure differential in the cell. There may be a contraction of surface area of the fluid-like erythrocyte analogous to surface tension of a raindrop. The contractile surface rounding up as a spherical cell is underpinned by a contractile cytoskeleton. Its triangles present a uniform tensile field radiating in all directions, just underlying the surface. The cytoskeleton is constructed like a tightly woven sweater (Liu and Derek, 1992). Possible invaginations of the surface by strains stretch the triangles out as equilateral triangles, pulling in series along various curved vectors with concerted tension.

I hypothesize the red blood cell as a biconcave disk (when un-deformed by strain) has greater pressure under the concave surface of the bulged circumferential cell surface. [Note that the convex outer surface, observed from the outside, is a concave surface facing inward into the endoplasm.] Endoplasm between the opposing *concave* dimples lies between two convex inner surfaces. In line with the famous findings long ago of Laplace, where $P_n - P_1 = 2T/r$, and r is the radius of curvature, less pressure should lie between the dimples. In the biconcave mammalian red cell, the hypothesized low pressure in the center would enhance the cell’s deformation, to bend about the middle, or to extend a firm forward surface into a capillary, while allowing any strain forces to dissipate in the purely viscous endoplasm.

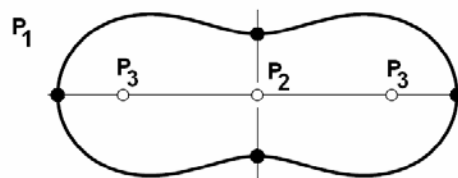


Figure 3. Cell Pressure. $P_3 > P_1, P_3 > P_2, P_2 = \text{low}$.

3.8. Viscosity and Hydrodynamics. The erythrocyte seems a projectile, when squeezing into tight places, whether moving against or penetrating blood flow. The advanced mammalian erythrocyte is surely no stream-lined projectile until it deforms. Mammal cells transport sufficient oxygen, but that may not always have been the case in the ancestral camels, which seemed to have reverted to an ancient ellipsoidal cell. That primitive shape is possibly due to great viscosity seen in *dehydrated* desert camels. They tolerate thick blood plasma (Schmidt-Nielsen, 1964).

In South American camels, often living at high elevations, their small cells, dense erythrocyte numbers, and rich Hb suggest that hypoxia may be involved with irregular ellipsoidal shape, although this was not claimed (Lewis, 1976). The reason alpine camels have the small, anucleate erythrocytes may simply result from inheriting them from ancestral desert camels. Large hoofed animals living in warm, open country, which is important in the evolution of Artiodactyls, must endure water and body heat problems. Generally all Artiodactyls have small erythrocytes (Gulliver, 1875) and rich Hb (which also may help transport some excess body heat, see Coates, 1975). Both plasma and cells bring inner heat from work and ambient sources to the body surface and to the lungs. In dehydrated camels, a biconcave cell would be maladaptive.

The small cell size, low Reynolds number, and huge surface to volume ratio in most mammal cells suggest there can be little movement except that caused by flow of the plasma. A fusiform shape of deformation is better in narrow capillaries, for traversing narrow slits, or working through crowded cell aggregations. In larger blood vessels, the red cells of mammals “snap back” rapidly into the biconcave form and move along without resisting the flow. The cell penetrating a narrow capillary vessel must be propelled against strains only by the blood pressure, perhaps focused from behind by bolus flow. The oxygen-transporting cell needs a streamlined form to absorb the resistance of the capillary wall. An analogy from Long (2004) of an ellipsoid in a cylindrical tube shows resemblance to his slender, elliptical weasel twisting about in a cylindrical burrow. Either a weasel, an ellipsoidal cell, or a biconcave cell deformed into an ellipsoid can “ooze” through tight places.

A visco-elastic fluid-like cell would slip through narrow spaces as easily as a raindrop (Schmid-Schoebein and Gaehtens, 1981; Thurston, 1996). Any strain force imparted into the endoplasm of such a red

cell is dissipated, but the endoplasm without help cannot re-attain its prior form (because it is purely viscous). The cytoskeleton, and to some extent the elasticity and surface tension of the membrane, can pop the shape back to normal. The dimples would likely reappear as two, rather than one deeper pocket. Three shallow dimples could appear. Dimples could move about rather than change the volume. This becomes a synthesis based upon experiments and deductions (Korpman, Bull, Brailsford, Canham, Palek, McMillan, Schmid-Schoenbine, and others).

4. Conclusion

Physical effects relating to bending, low pressure between dimples, the effects of inertia, surface/volume exchange function, and the role of energy conservation all affect the dynamics of the erythrocyte, which in mammals extrudes the nucleus and loses marginal bands. “Visco-elastic” is weak resistance to strain and dissipation of strain energy. A cell assuming a shape of minimal bending energy does not rule out some contractile properties of the liquid-like membrane (even surface tension), but especially the tensile effect of a curvaceous cytoskeleton. The deformed erythrocyte “oozes” through small openings or tubes. The biconcave form of mammals avoids strains and rides with the current, while maintaining a high surface area per unit volume. It kites along with rapidity and little wear. Noting a few peculiarities related to high or low metabolism, or possibly for surviving dehydration or hypoxia, a general specialization of the mammalian erythrocyte seems a driving evolutionary force in mammalian evolution.

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