→ + Gross 9/19.79
cc: S. Franklin 9/28/79

Summary of Highlightw

"Cell Injury in Shock, Anoxia and Ischemia"

R A.Cowley, M.D. and B.F.Trump, Editors

September 17 - 19, 1979

The Tidewater Inn, Easton, Maryland

Probably for the first time ~~authorities~~ experts in cellular pathobiology, shock, ischemia, and myocardial infarction, central nervous system, ~~stroke~~ ingury, etc., discussed in depth common problems. The results make it clear that many if not all the important problems in these diseases have common sources at the cellular and subcellular levels.

A prime example of this is the emerging importance of calcium regulation in this process. Dr. Carafoli discussed the principles of calcium regulation in normal cells and Dr.Trump showed evidence of its involvement in cell injury. In the normal cell Carafoli emphasized the importance of mitochondria in regulation of cytosol Ca++ which continually leaks into the cell. In muscle cells the sarcomplasmic reticulum also contributes. Dr.Trump pointed out that in the normal cell calcium has many functions including the stabilization of the cytoskeleton and and microfilaments as well as ~~in~~ modifying cell-cell communication, and cell junctions in tight epitheleal layers. In injured cells ~~in~~ with anoxia, ischemia or sepsis, calcium regulation fails. In ischemia this appears to be primarily due to loss of mitochondrial regulation whereas in septic shock increased plasma membrane permeability may contribute. Increased cytosol calcium also causes cellular contraction and dissociation of cell-cell interactions which could contribute to increased vascular permeability. It was speculated at the meeting that this might be modified by methylprednisolone. The increased cytosol calcium may also activate cytoplasmic phospholipases which

cause irreversible membrane damage. Dr.Sayeed also commented on the importance of membrane pumping systems in hemorrhagic shock in the liver pointing to the inactivation of the sodium-potassium ATPase . While this appears to be a primary result of an energy deficit in the cell we cannot , at present, exclude factors which might also damage the cell membrane. Dr.Mergner, discussing myocardial infarction, also emphasized the role of phospholipases in modifying bioenergetic mechanisms, especially as phospholipase affect cell membranes. Dr.Reimer also discussed lack of volume and ion regulation as a key factor in the onset of irreversibility in experimental myocardial infarction. It seems clear that future interventions should be developed to modify intracellular phospholipases, retard entrance of intracellular xxx and/or to inhibit the effects of calcium. The role of lowered extracellular pH in protecting cells against anoxia and in vitro systems could relate to these effects. Increased autophagocytosis is a characteristic of sublethally injured cells, especially in chronic sepsis. Dr. Bessman emphasized the endocrine machinery set into effect which is predominantly catabolic and Dr.Cowley and Jones commented on the numerous autophagic vacuoles turning over cells in the liver and pancreas. Once again Trump pointed out the possible role of microtubular interference in this process since calcium ionophores can reproduce the same effect and since Ca results in microtubular dissolution. It is clear that widespread autophagocytosis is the probable mechanism of protein turnover in liver and can easily be induced by administration of glucagon. Cerra and Siegel emphasized the tremendous elevation of serum glucagon in septic shock which fits together very nicely. Modification of the calcium regulating protein calmodulin could be another important factor.

Discussions of therapy in shock were extensive. Clark presented details of recent experiments on fluorocarbon emulsions which are able to sustain life in rats subjected to hemorrhagic shock. Complete blood replacement with these artificial bloods is possible. The concent mentioned by Clark, that these should not be considered as blood substitutes but as resuscitation media which, in future, may well be far superior to blood or blood components. This was also alluded to by Wilson in a discussion of future treatment of shock inwhich the need for artificial organs, including those for the heart and liver are possible but presently held up by lack of surfaces which resembel endothelia. With Clark's solutions and their derivatives in the future, such problems would disappear, ~~and~~ possibly a major breakthrough. In the area of cyclic nucleotides, Murad reviewed the subject and suggested that important interactions occur between cyclic GMP and calcium (see above) can occur. He also mentioned a possible mechanism for nitrites, and nitroglycerin ~~&~~ and related compounds on vascular dilatation through free radical mechanisms. The entire area of vascular mediators was reviewed by Lefer who stressed the resurgence of interest in angiotensin, a new analog with which he is working PTA2 which blocks thromboxane, and the continuing importance of platelet activation.

Monitoring of patients is entering a new era. The era of cardiovascular monitoring is essential, obviously, for resuscitation and maintenance , is soon to be replaced by other types of biochemical and cellular studies on tissues rather than on blood. It was stressed by both Bergman and Wilson that looking at blood is not satisfactory and that we need to improve our biopsy ~~and~~ methods for enzyme analysis and analysis at the ultrastructural level. Advances are also being made in transfusion therapy. Ben Dawson reviewed the

development of a committed portion of the medical center Blood Bank to a large ICU stressing the use of untyped O+ blood which does not lead to fatal reactions and which has been very successful in resuscitating patients with blood in large quantities.

Septic shock was extensively discussed by and of particular interest was Dr.Mela's discussion of the role of sepsis in the central nervous system in modifying permeability and interfering with CNS metabolism. This is something that needs much further study.

The role of the liver as one of the important organs in multiple organ failure was stressed by Dr.Cowley and Dr.Cerra. Severe liver alterations occur in all severely injured patients. This was previously unrecognized but now with modern biochemical and electron microscopic techniques severe energy deficits and organelle alterations occur in hepatocytes. In septic shock the changes are much more severe with heightened turnover, increased autophagic vacuoles resulting in large residual body typesa of lysosomes. Cerra stressed that hepatocellular alterations may contribute in a rather direct way to the genesis of septic shock. This could involve failure to modify agents resorbed from the GI tract through the portal system. The role of the liver was also strongly emphasized by Dr.Ozawax who showed that hemorrhagic shock in jaundiced animals had a major influence in a detrimental direction on the energy deficit.

We currently know relatively little about the effects of shock on the gastrointestinal epithelium. Mittermayer reviewed current data which reveal extensive changes; however early changes, especially at the subcellular level, remain to be defined and need more extensive research. This could be a fruitful area of research since introduction of agents orally or by gastric tube, which could modify the epithelium and its permeability might be of interest.

The lung was discussed extensively by Webb, Mittermayer and Sibbald. Rather extensive changes occur in the lung in shock which cannot be ascribed to therapy. There are changes in permeability, to particles, and the question of colloid or not was discussed. Webb pointed out that although he added albumin to his hypertonic saline resuscitation fluids its effects were not certain. Since capillary permeability does increase markedly and the pore size is only beginning to be investigated, for example by Sibbald, more work is needed to evaluate this question. We don't know still the site of increased capillary permeability in the shock lung or its cause. It could be arteriolar, capillary or venular and a possible revival of histamine-induced permeability change was suggested by Sibbald. Other possibilities include the effects of C5A on granulocytes, granulocyte lysosomes secretion;, super oxide formation, etc.

The current ideas on acute renal failure in very normal environments were discussed by McDowell and Flamenbaum. In animal models It appears that both toxic and ischemic induced acute renal failure develop through a renin-angiotensin tubular glomerular feedback lesion. The assertion is that the initiating event is a reversible damage to the proximal convoluted tubule which results in defective sodium resorbtion resulting in increased sodium and chloride at the macula densa with feedback renin generation, decreased angiotensin formation and diminished glomerular filtration vasoconstriction. Flamenbaum illustrated how modification of the furosemide method with loop diuretics such as Fluorocymide forms the basis of their possible effects in the early reversal of incipient acute renal failure. More work could be done since some toxic induced

acute renal failure could be reversed by appropriate compounds and other compounds which modify the renin-angiotensin system including inhibitors of the reaction could modify ischemic acute renal failure. Flamenbaum also emphasized that toxic induced acute renal failure is approximately half of acute renal failure in acute care units.

In-depth discussions were held regarding the pathophysiology of head and spinal cord injury and stroke. A consensus was reached that the problems here are very similar to those in other organs. Once again, we are dealing with problems at the endothelial cell level in terms of decreased cell adhesion, increased endothelial permeability and the effects of ischemia, on parenchymal cells, neurons, astrocytes, etc. Ransohoff presented preliminary data suggesting a role of antioxidants in preventing increased capillary permeability in spinal cord injury and Jones showed good evidence that there is a gated permeability process in the arachnoid villi which responds normally by increasing the gates to increase intracranial pressure both but which in injurious situations may

---

meeting to have such diverse experts together discussing the commonality of these events.

The modification of myocardial infarction was discussed by Muller. Hyaluronidase improves situation in both dogs and patients, nitroglycerine is questionable, glycose-insulin -K, KIK still not clear. Nifedipine markedly alleviates Prinzmetal's angina - should be tried in shock. Spasm in coronary arteries may be more important than thought previously.

A consensus was reached at the meeting on protective effect of KIK in septic shock. Mechanism still unknown. Demling had some data on endotoxin-treated lungs in sheep. KIK rapidly modified the effects.

Another role of ¤ corticosteroids in experimental shock was mentioned by Dr. Jones who reported that MPS inhibited the tremendous autophagic vacuole response that occurs in the rat liver following shock or glucagon.