

Public Lecture by Dr. Geert Schmid-Schönbein
The Search for the Trigger Mechanism of Heart Attacks or Strokes
July 18, 2001 at 6:00 p.m. in the Garren Auditorium, Basic Science Building
Sponsored by the Sam & Rose Stein Institute for Research on Aging, UCSD

In many cardiovascular diseases, including heart attack, cerebral stroke, and even in individuals with just risk factors for cardiovascular disease, such as smokers or individuals with chronic infections, a set of inflammatory mediators can be detected in the blood circulation. These inflammatory mediators are not detected to any significant degree in young health individuals without cardiovascular complications or individuals without cardiovascular risk factors. The inflammatory mediators are detectable in blood plasma and may be present long before actual serious complications arise which may require interventions and hospitalization. The inflammatory mediators produce cell activation in large and small blood vessels, which leads to many forms of cell and tissue dysfunctions and even frank cell death. These mediators produce a form of non-infectious inflammation that can cause many complications, such as lesions in the large arteries or occlusion of blood vessels in the microcirculation. But the source of these inflammatory mediators and their molecular identity has remained unknown. I will report about a recent series of research projects that is designed to find the origin of these stimulating mediators. It is one of the interesting detective stories in medicine. Identification of these inflammatory mediators will provide the knowledge necessary to facilitate early intervention and improve our ability for prevention of cardiovascular disease and perhaps even other diseases.

Our research program was focused on physiological shock, one of the most difficult conditions to control. In shock especially high levels of the inflammatory mediators can be detected and healthy organs may fail in rapid succession. A number of students have made contributions to this problem. Dr. Erik Kistler has discovered a source for the inflammatory activating factor derived from a unique and also surprising source, the pancreas and its digestive enzymes. Our collaborator, Dr. Toni Hugli of the La Jolla Institute for Molecular Medicine, and Ms. Anasthasia Sofianos identified a way to purify the inflammatory mediators. Dr. Hiroshi Mitsuoka has discovered a way to block the production of the activating factors in shock, a procedure that prevents organ failure in experimental animals. Mr. Alexander Penn, a graduate student in Bioengineering, is studying the molecular structure of some of the inflammatory mediators and their mode of action.

Our results point to a surprising sequence of events involving the *pancreas*. Hidden deep below the stomach, the pancreas produces besides insulin the digestive enzymes we require for normal digestion of our daily food. The digestive enzymes are designed to degrade all biological molecules we consume, lipids, carbohydrates, proteins and nucleotides. What prevents pancreatic enzymes to digest our own tissue, even though they can do so from a biochemical point of view? The most likely mechanisms that prevent self-digestion is compartmentalization of the enzymes. Pancreatic enzymes are restricted to the lumen of the intestine by a specialized epithelial cell lining in the lumen of the intestine. But this usually tight cell lining may become permeable in situations such as shock so that the digestive enzymes can enter into the wall of the intestine and digest our own tissue. Such an event precipitates shock and the productions of inflammatory mediators. Shock is the consequence of self-digestion process. Out of these observations arise many new possibilities to interfere with cell activation in the circulation. We will explore new methods to prevent the pancreatic enzymatic attack on our own tissue, to block the inflammatory mediators that are produced when our own intestine is being digested, and to develop new methods for their detection and removal from the circulation.

Some recent references:

- Kistler, E.B., Hugli, T.E., Schmid-Schönbein, G.W.: The pancreas as a source of cardiovascular cell activating factors. *Microcirculation*, 7:183-192, 2000.
- Kistler, E.B., Lefer, A.M., Hugli, T.E., Schmid-Schönbein, G.W.: Plasma activation during splanchnic arterial occlusion shock. *Shock*, 14:30-34, 2000.
- Mitsuoka, H., Kistler, E.B., Schmid-Schönbein, G.W.: Generation of in vivo activating factors in the ischemic intestine by pancreatic enzymes. *Proc. Nat. Acad. Sci. U.S.A.*, 97:1772-1777, 2000.
- Kistler, E.B., Hugli, T.E., Schmid-Schönbein, G.W.: The pancreas as a source of cardiovascular cell activating factors. *Microcirculation*, 7:183-192, 2000.