GENERAL DISCUSSION ON TURNOVER AND ELASTOLYSIS

Dr. Yu: I would like to ask Dr. Robert and Dr. Hornebeck to clarify their studies of human aorta which apparently breaks down continuously. I hope this only occurs in the diseased aorta. Do you think a normal full grown animal aorta displays this kind of turnover through the action of elastolytic enzymes?

Dr. Robert: There is some evidence in favor of that. First of all this enzyme is present in several species. Not only in all human aortas which were studied by Dr. Hornebeck, but it is present in the aortas of rabbit, dog, mouse, etc. Then there are several studies which show the presence of those fine fibers appearing in the aging aorta. So what really is not resynthesized during the lifetime are the concentric lamellae. Yet fine fibers form apparently during the whole lifetime. Careful studies done on the rat, for instance, during the whole life span show that elastin content increases nearly linearly at a slow rate. So I think that elastin really may have a turnover.

Dr. Yu: I raised this issue because there are a large amount of protease inhibitors present in the tissue. These inhibitors control most of these elastolytic enzymes so that perhaps the aorta might continue to synthesize elastin. I doubt that the enzyme is able to attack under normal conditions, only pathological conditions.

Dr. Robert: Well I'm not as optimistic. Some years ago we did experiments with Dr. Turino. We injected elastase intravenously to puppies in amounts which could be easily complexed by the circulating inhibitors. Still considerable damage was done to the elastic fibers in the lungs and in the aorta. In addition, I think that as heterogeneous kinetic studies showed, the fact that the enzyme can be absorbed on its substrate would make it very difficult for any inhibitor to completely prevent hydrolysis. It is much more difficult to dissociate the enzyme absorbed on elastin than it would be to have a homogeneous kinetic system of an enzyme, inhibitor, and substrate. That is why I think that even the normal concentrations of inhibitors are not sufficient to prevent elastolysis.

Dr. Cleary: I have two pieces of information that are relevant to two different aspects of the dis-
cussion. We have, in fact, measured the absolute amount of sodium hydroxide prepared elastin in the thoracic aorta of rabbits of a single breed from a single colony. There is evidence of continuing synthesis of both elastin and of collagen for 140 weeks. That is true also of the abdominal aorta, although the rate of synthesis in terms of absolute amount is less. I feel that if you want to demonstrate the presence of elastolysis, it is not proper to use evidence of continuing synthesis as an indication of elastolysis, because there is continuing accumulation of insoluble elastin under normal circumstances.

My second comment relates to the comments that Dr. Hornebeck made about atherosclerosis and the content of elastin. The distribution of elastin and collagen along the aorta is very different. The thoracic aorta has a high content of elastin; the abdominal aorta has a low content of elastin and a relatively high content of collagen. With intima-media preparations, the selection of your sample will very much determine the type of elastin contents that you get in atherosclerotic lesions. Atherosclerosis is usually much more marked in the abdominal aorta than it is in the thoracic. With the subsequent development of the lesions you get more severe type lesions, grade 2 and grade 3, in the abdominal aorta while there may be only grade 1 and grade 2 in the thoracic. In your selection of samples for analyses, you would need to be very careful to select them all from the same location.

Dr. Robert: I think what is important to stress is that the elastase determinations Dr. Hornebeck described were done on aortic samples which were not directly involved with the lesions; and, as you know, elastin degradation is going on in a diffuse fashion along the whole length of the aorta, and the lesions are always localized. So there are two distinct phenomena. One can try to correlate them just to show that general elastolysis can somehow be the factor which predisposes the formation of the plaque. We don't claim that sort of causal relationship between these two phenomenon does exist.

Dr. Anwar: My comment is of a very general type. Is it true that any enzyme which attacks or solubilizes elastin may have as its function breakdown of elastin? That might be an erroneous conclusion under certain conditions because we know pepsin will solubilize elastin; yet its function is not to break down elastin.