

Introduction: Target Organ Meeting on the Cardiovascular System

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This meeting represented the first time that the cardiovascular system, *per se*, had been the focus of a conference on toxicology. The approach to such potentially broad topics must necessarily be somewhat restrictive because of the limited time available for platform presentations, and finite human endurance, both in the area of assembling and presenting the program, and in the equally important area of the participating listeners. For these reasons we chose to emphasize the heart in this conference in an effort to better cover a limited area, rather than superficially cover too much.

The plan of the program was first to review certain recent advances in the biology of the heart that are particularly relevant to cardiovascular toxicology. The program moved from the structural and functional foundations through which evidence of cardiovascular toxicity is expressed, to a variety of examples of chemical injury to the cardiovascular system. The third session focused on methods of study of the cardiovascular system with further examples of expressions of cardiovascular toxicity. The final session was devoted to discussions of the relevance of the preceding to man, the ultimate beneficiary of the scientific inquiry. Figure 1 illustrates the progression of ideas from the target organ to functional mechanisms through which cardiovascular toxicity might be expressed. Within the heart we are dealing with contractile and conductile myocardium, two somewhat different types of tissue of identical embryonic origin. The distinction is of somewhat limited usefulness, however, since the contractile myocardium conducts excitatory impulses, on the one hand, and the conductile myocardium is not completely devoid of limited

contractile capability, on the other (1).

Mechanisms through which cardiovascular toxicity could be expressed may include chemical interactions with various subcellular targets, and indirect effects, especially as they bear on cardiac structure and function, as suggested in Figure 1.

A working definition of cardiac toxicity is contained in Figure 2. This author believes that reversible structural and functional impairment should be included within the full scope of cardiac toxicity because structure and function must inevitably be interdependent. Electron microscopy has provided striking examples of ultrastructural changes accom-

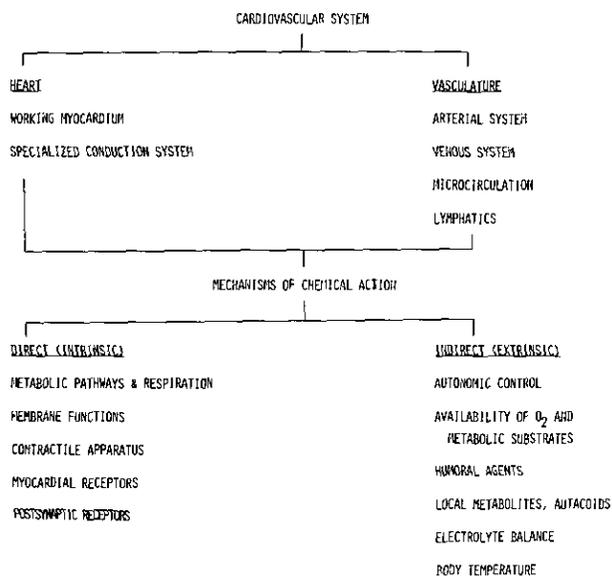


FIGURE 1. Flow chart illustrating the basic subdivisions of the cardiovascular system and showing how both direct and indirect mechanisms of chemical action may lead to expressions of biological activity.

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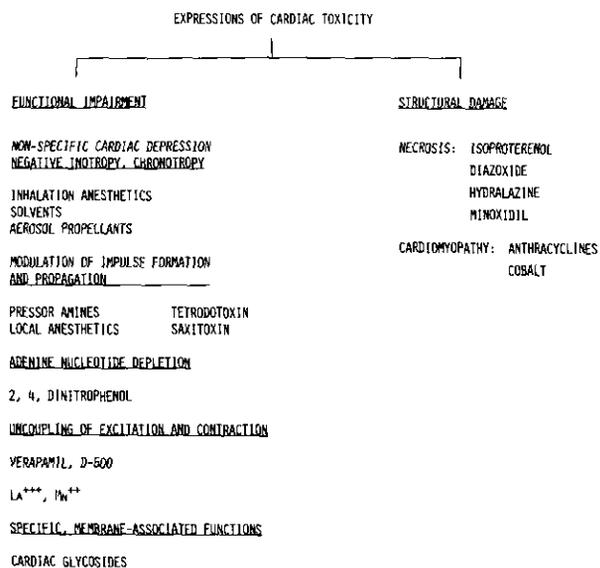


FIGURE 2. Expressions of cardiac toxicity may take the form of either or both functional and structural abnormalities.

panying functional derangements that are undetectable by light microscopy. An example is the alteration of the cardiac mitochondrial cristae configuration that is seen in the presence of myocardial depression during the inhalation of $CBrF_3$ (2).

Expressions of the unwanted effects of chemicals in the mammalian organism may be the consequence of what may be rather nonspecific interactions with the target organs. The cardiac depression that accompanies exposure to a wide variety of lipid-soluble compounds such as solvents and vaporizable anesthetics may be the consequence of their preferential distribution to hydrophobic subcellular regions such as the lipids of subcellular membranes and hydrophobic regions of globular proteins.

Nonspecific mechanisms may underlie functional disturbances in not only mechanical, but also elec-

trical performance of the myocardium. The electrical performance, on the other hand, may be altered by the actions of chemicals that act in quite specific fashion at sites important to the regulation of transmembrane ion fluxes.

Calcium antagonists may interfere with excitation-contraction coupling by blocking the event responsible for making contractile calcium ions available to intracellular troponin binding sites. The actions of the highly toxic cardiac glycosides are thought to be mediated by their involvement in certain membrane-associated functions that modulate contractile force.

Myocardial depression can result from a variety of effects of chemicals on intermediary metabolism, of which the uncoupling of oxidation from the phosphorylation of ADP by 2,4-dinitrophenol is an example.

Irreversible structural damage to the myocardium can be produced by high doses of certain pressor amines and vasodilators. Antineoplastic drugs and cobalt produce comparable results but certainly through different mechanisms.

The variety of expressions of cardiovascular toxicity, especially in the heart, is great, and deserving of the directed attention of the scientific community. It is the hope of the organizers of this conference that the exercise will serve to focus the attention of the community of toxicologists and other interested scientists on cardiovascular toxicology as an area of great scientific interest, and potentially significant public health importance as well.

REFERENCES

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