INTRODUCTION

The heart talks through the pulse. The heart doesn't talk any more and the vessels, which originate out of the heart, are silent.

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Sudden and chronic heart failure was recognized by the ancient Egyptians as being life threatening. This is clear from discoveries, made by George Ebers in 1890, of books written by them about the heart.

In recent years cardiac failure has become a major concern for clinicians. The incidence of heart failure in the USA was about 400,000 per year in 1983 [1], which is similar to the rate in Europe, whereas, in South America, Chagas' disease, which can result in heart failure, may be present in 10 million people [1]. The main etiology in industrialized countries is coronary artery disease with systemic hypertension. Since the incidence of heart failure correlates directly with age [2] and since life expectancy is increasing in most developed countries, an increasing number of patients with cardiac failure are awaiting treatment.

Cardiac failure is usually characterized as the inability of the heart to pump blood at a rate sufficient to meet the needs of peripheral tissues. In terms of hemodynamics, congestive heart failure may be defined as a reduced cardiac output despite an elevation in ventricular filling pressure. It has, however, been recognized that this simple definition does not cover the complexity of all hemodynamic and neurohumoral alterations occurring in congestive heart failure.

The complex interrelationship between the heart and the circulation, and the actions of each part of the circulatory system, including the sympathetic nervous system and the endocrine system, have evolved in two stages. The first stage followed an investigation by Braunwald et al. [3] during the 1960s on the mechanism of contraction of the normal and failing heart. Contractility, afterload, and preload were newly defined on a physical basis. The second stage occurred when it became known that the heart is not only connected anatomically to the circulation, but it is also connected functionally by positive and negative feedbacks from the whole circulatory system, including the central and peripheral nervous system. Application of

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the theory of feedback has considerably improved the understanding of events occurring during the development of heart failure. Intense study of congestive heart failure has shown that the interrelationships between its clinical symptoms are more complex than was once thought. Usually, systolic function is impaired in myocardial failure, while diastolic impairment develops consecutively and is seldom the sole cause. The activation of neurohumoral mechanisms, including the sympathetic nervous system, the renin-angiotensin-aldosterone system, and the antidiuretic hormone-vasopressin system, is characteristic of cardiac failure and may alter venous return (preload) and peripheral resistance (afterload) in a way that maintains an adequate cardiac output. This activation acts as a compensatory mechanism and may be the reason that the characteristic hemodynamic changes associated with cardiac failure do not necessarily correlate with the clinical symptoms.

While it remains to be clarified how these activated neurohumoral mechanisms may affect the heart and contribute to the clinical severity of symptoms, there is no longer a dispute about the role of the heart itself. Experience gained through heart transplants has shown that replacing the heart with a donor organ almost immediately reverses all the abnormalities that existed prior to the operation and returns the patient's exercise tolerance to normal. Thus, in terms of pathophysiology and therapy, the key question is not whether the inability of the heart to pump blood is the primary cause, but whether peripheral responses may also be critical in determining symptoms and prognosis.

Despite ongoing basic research into biochemical changes in the myocardium and the relative impor-

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tance of the neurohumoral mechanisms that affect the heart and the periphery, treatment of the clinical syndrome of cardiac failure has focused in two directions.

The first direction of investigation was the improvement of contractility by positive inotropic drugs. The discovery of digitalis glycosides by Withering [4] was a major advance. This was followed by the discovery of β -adrenoreceptor agonists, noradrenaline, and dobutamine, which are still used to treat patients with heart failure. Since digitalis has a comparatively low therapeutic efficacy and a high potential toxicity, and noradrenaline and dobutamine are only administered intravenously, the search for other therapeutic agents has continued. As a result, in 1978 amrinone, the first nonglycosidic agent, was introduced, and this has been followed by the introduction of a number of other nonglycosidic agents.

The second direction of investigation for the treatment of heart failure was to find substances that antagonize the changed neurohumoral responses. These include peripheral vasodilators and angiotensin-converting enzyme inhibitors (ACE-inhibitors).

Of the different orally administered positive inotropic drugs studied thus far, most experience has been gained with regard to the pharmacology, mechanism of

action, and clinical effect of the phosphodiesterase inhibitors [5, 6]. This symposium focuses on one of these compounds and is aimed at presenting the latest information on phosphodiesterase inhibitors in the light of epidemiology, central and peripheral physiology, and the therapy of acute and chronic heart failure.

References

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