

## Regional Focus Series: Progress of Clinical Science in Japan

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### Editor's preface

In the Spring of 1993, Professor A. M. Heagerty, Deputy Chairman of *Clinical Science*, asked me to edit an overview of developments and achievements in clinical science in Japan by experts in selected fields. I accepted this proposal without much thought. However, when I started, I faced tremendous difficulties as editor: how would I select the topics, and who would be suitable contributors. Finally, I decided by my own dogmatic judgment. I

invited 10 experts from different fields of clinical science, mainly internal medicine, and asked them to describe their own work and also other relevant clinical research in Japan. Of course, this review is only an introduction to part of the research taking place in Japan. I hope that the readers of this Journal will become aware of the scientific fields in Japan and will spend a short time comprehending the progress of clinical research in Japan.

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### Molecular mechanism of cardiac hypertrophy and failure

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Cardiac hypertrophy and the resulting heart failure due to valvular disease and hypertension is one of the main causes of mortality and morbidity. The heart first responds to an increased work load by an alteration in function, and, secondly by an increase in muscle mass and changes in gene expression. Many lines of evidence have suggested that activation of a new programme of gene expression in the overloaded heart is important to maintain cardiac function as an adaptation. These genes can be divided into two classes, immediate-early genes (IEG) and late-response genes. As an example of the induction of IEG by pressure overload, the expression of proto-oncogenes, such as *c-fos* and *c-myc*, was first reported in the rat heart *in vivo* [1]. In addition to these known IEG, a number of genes rapidly change their levels of expression in the heart by haemodynamic overload [2].

The contraction unit of the myocardium is the sarcomere, which comprises seven major proteins and several minor ones. All of these major proteins have multiple isoforms, and some isoforms are selectively increased at the transcriptional level in cardiac hypertrophy. This response is characterized by the re-expression of the protein isoforms which are ordinarily expressed in the embryonic heart but not in the adult heart [1, 2]. As a late-response 'fetal' gene, cardiac myosin heavy chain (MHC) is best studied both at the physiological and molecular

levels [3, 4]. In cardiac hypertrophy induced by haemodynamic overload, the myosin isoform is changed from the  $\alpha$  to the  $\beta$  form [5, 6]. The transition from the  $\alpha$  to the  $\beta$  form decreases the initial speed of shortening, but improves the efficiency of contraction for an equivalent amount of work, suggesting that it might be an 'adaptation' of the cardiac muscle. This reprogramming of gene expression in the heart by haemodynamic overload is not limited to contractile proteins, but includes other proteins such as creatine kinase and atrial natriuretic peptide.

In contrast to these up-regulated genes, the transcription of some genes is down-regulated by haemodynamic overload. One of these genes is that for the  $\text{Ca}^{2+}$ -ATPase in the sarcoplasmic reticulum. The levels of mRNA for  $\text{Ca}^{2+}$ -ATPase are gradually decreased by pressure overload in the animal model [7] and a reduced expression of  $\text{Ca}^{2+}$ -ATPase was observed in failing and fetal hearts [7]. This decrease in mRNA levels is accompanied by reduced protein levels, which may be, at least in part, the cause of the abnormal  $\text{Ca}^{2+}$  handling in hypertrophic, failing and fetal hearts.

To understand the mechanisms by which haemodynamic overload alters the expression of these genes, an *in vitro* loading system employing cultured quiescent cardiomyocytes was developed [8]. Neonatal rat cardiocytes were cultured in deformable silicone dishes with defined serum-free media and a mechanical load was imposed by stretching the adherent cells. Myocyte stretching stimulated the expression of IEG and 'fetal' genes, followed by an increase in amino acid incorporation into proteins [8, 9]. Transfection and pharmacological experiments suggest that the activation of protein kinase C is necessary for the expression of these genes.