PUBLISHED WORKS SUBMITTED TO THE UNIVERSITY OF ADELAIDE FOR THE DEGREE OF DOCTOR OF SCIENCE

ROBERT VANDONGEN
BMedSc(Hon),MD,FRACP

Associate Professor of Medicine
University of Western Australia
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The work can be broadly divided into the following categories:

(1) Renin-Angiotensin System

(2) Experimental Renal Hypertension

(3) Physiology and Metabolism of Catecholamines

(4) Epidemiology of Blood Pressure and Hypertension

(5) Studies in Eicosanoid and Phospholipid Metabolism

(6) Therapy in Hypertension and Other Publications

Each category will be dealt with separately in outlining what I consider to have been my principal and most significant contributions. I wish to emphasise that a majority of my publications are the result of collaborative efforts with several colleagues as is to be expected from the varied and multidisciplinary nature of the studies. However in each case I believe my contribution to have been a major one in terms of conceptual, supervisory and resource input. The list of authors is generally headed by the name of the person primarily responsible for the work which was myself in many of the earlier publications. As my research involvement changed direction to a more supervisory role, it has been my policy to award senior authorship to the research students and fellows responsible for the project. My senior co-authors on several publications, Professors Armstrong, Beilin and Masarei, are usually listed in the order of their contribution to the study.

(1) Renin-Angiotensin System

I commenced my research career in this area, it being the subject of my MD thesis and an area actively pursued during subsequent post-doctoral studies and culminating in the identification of adrenoceptors regulating renin secretion.

The first evidence of an inhibitory affect of α-adrenoceptors originated from this work and this was followed by my observation that inhibitory mechanisms were calcium-dependent. This finding led to the hypothesis linking renin secretion to the intracellular events initiating smooth muscle contraction. A recent review article* stated that this work has been "chiefly responsible for the substantial advances made in our understanding of renin secretion". Further studies explored the relationship between renin secretion and the renal prostaglandin system, demonstrating the independence of β-adrenoceptor and frusemide-induced renin release but supporting an important role for renal prostanoids in modulating the vasoconstrictor effects of pressor substances.

*Fray, J.C.S. et al. Calcium and the Control of Renin Secretion Endocrine Reviews 8:53-93, 1987

(2) Experimental Renal Hypertension

This major area of interest has recently focussed on the mechanisms operating during the reversal of renal-clip hypertension in the rat. This is achieved by removal of the constricting clip from the renal artery of a solitary kidney in rats which have been hypertensive for several weeks. Restoration of normal blood pressure occurs within 24 hours and may be apparent as early as 30 minutes after unclipping.

Our studies have clearly demonstrated an association between the fall in blood pressure and enhancement of eicosanoid synthesis in blood, kidney and vascular tissue. We have made the unique observation that this increase in eicosanoid formation is accompanied by release of the potent vasodepressor phospholipid 1-O-alkyl-2-acetylglycerophosphocholine. This lipid, also known as PAF (Platelet Activating Factor), has a wide spectrum of

activities including platelet aggregation, and was first measured in plasma by a method developed in our laboratory. These findings have led to the hypothesis that renal hypertension may be, at least partially, attributable to an inhibitor of phospholipase activity generated in ischaemic kidney tissue. Relief of ischaemia by unclipping reactivates phospholipases leading to increased availability of arachidonic acid and PAF precursors, resulting in increased eicosanoid and PAF synthesis.

(3) Physiology and Metabolism of Catecholamines

The major thrust in this area has been a critical evaluation of the role of sulphate-conjugation, a previously neglected pathway of catecholamine inactivation, in the regulation of the plasma levels of free catecholamines and in the handling of dietary amines by the gut. These studies have demonstrated the importance of sulphate conjugation in modulating plasma free catecholamines in situations where there is excessive sympathetic nervous activity.

The pivotal role of the gut and liver in inactivating potentially hazardous quantities of vasoactive dietary amines has been highlighted and emphasized by an examination of the effect of competitive inhibitors of sulphate conjugation. The considerable interindividual variation in the disposition of dietary amines has been studied in some detail and appears to be due to genetically determined characteristics of phenolsulphotransferase activity. These studies are complimentary to our work on diet-blood pressure relationships.

We have reported highly significant differences in plasma amines between males and females and provide evidence that this may be due to an oestrogen effect on enzymatic degradation pathways.

A differential effect of β-adrenoceptor blockers with andwithout intrinsic sympathomimetic activity on plasma catecholamine levels has been demonstrated both at rest and in relation to changes in sympathetic nervous activity. These findings are highly relevant to furthering understanding of the mechanism whereby β-blockers alter lipid metabolism, through a putative adrenoceptor inhibitory effect on lipoprotein lipase, as well as providing

indirect evidence for cardiac output being an important determinant of catecholamine clearance.

(4) Epidemiology of Blood Pressure and Hypertension

This significant and major component of my research contributions is one where there is considerably interaction amongst senior collaborators. These projects have followed the traditional epidemiological approach, starting with cross-sectional population surveys followed by specific intervention studies and ending with attempts to identify mechanisms. The intervention studies with vegetarian diet and alcohol have been internationally recognised for their originality and scientific merit. The studies have been extended, particularly with respect to alcohol, to examine possible mechanisms involved in the now well documented pressor effect of alcohol. These investigations have clearly shown involvement of sympathetic and renal pressor systems in the acute cardiovascular response to alcohol and provide important clues as to the long term consequences of such involvements. The studies have been coupled with an examination of lipoprotein metabolism in response to alcohol and a critical evaluation of the prostaglandin-kinin systems as a possible mediator of the blood pressure response to dietary potassium. These studies also demonstrate very clearly the integration of basic laboratory methodology with clinical and epidemiological approaches to human pathophysiology.

(5) Studies in Eicosanoid and Phospholipid Metabolism

These more fundamental and biochemically orientated projects are designed to provide information about the effect of dietary fats on the biosynthesis of eicosanoids (including prostanoids and lipoxygenase products) and certain phospholipid mediators of platelet aggregation, leukotaxis and inflammatory responses. These studies again form part of the collaborative approach to research in which I have played a leading role particularly in relation to the effect of the omega-3 polyunsaturated fats on eicosanoid metabolism, the synthesis of Platelet Activating Factor and the production of leukotrienes from leukocytes. These products have required the development of a range of biochemical measurements of arachidonic and eicosapentaenoic acid,

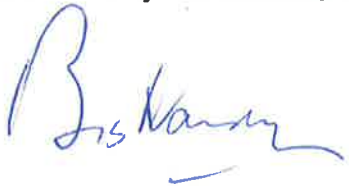
metabolites, including the utilisation of HPLC techniques for leukotrienes. This work is obviously closely linked with the studies in experimental hypertension and has been recently expanded to include investigations into the effects of fish oil diets on cholesterol metabolism. These studies have yielded the important finding of a selective effect of fish oil in increasing the plasma level of the subfraction HDL_2-cholesterol. This represents one of the first demonstrations that a nutrient can influence the synthesis of this lipoprotein which exerts a strong protective affect against the development of cardiovascular disease.

(6) Therapy in Hypertension and Others

These studies are complementary to the projects in clinical and experimental hypertension and the regulation of blood pressure control. The trials have been designed to provide additional information, particularly on aspects of catecholamine physiology. Amongst "others" are included works in experimental embryology and in physical anthropology based on studies whilst an undergraduate medical student, as well as several papers recently in press.

I submit that these published works are satisfactory evidence that I have made an original contribution of distinguished merit adding to knowledge of the biochemical, physiological and clinical basis of cardiovascular medicine, and hypertension in particular.

Publications 1-4 formed part of my MD thesis; otherwise the work has not been submitted for a degree in any University.



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