On Stress Disease and Evolution: A unifying theory

Graham W. Boyd


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Email address for correspondence: graham.boyd@uwa.edu.au

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The original cover photograph above shows points of focal constriction in a branch of the superior mesenteric artery in the anaesthetised rat following an intravenous injection of noradrenaline (G W Boyd and A C Yong, personal observations). A major contention of the present thesis is that sympathetically-activated stress-induced arterial constriction of this type is a fundamental initiating factor underlying many disease processes, and has an important bearing on cancer pathogenesis and evolutionary mechanisms – through ischaemic destabilisation of a genome composed essentially of viral genetic modules.
Dedication

To My Father, Bush Logician

The Search is not for Knowledge, but through it Understanding

Acknowledgements

I wish to thank Lynn Davies of the University of Tasmania Medical school library for her help in establishing the eprint version of this manuscript, and my wife, Judith for her support and encouragement throughout the preparation of this 2nd edition of the book.
Other works by the Author on Mechanisms in Disease


Department of medicine, University of Tasmania, Hobart, Australia
On Stress Disease and Evolution

Abstract

I present a perspective on disease mechanisms developed over my years of clinical experience. In Part I, I look at the history of data synthesis in medicine and medical science, and find it to be rather haphazard. I suggest a new way of building up the clinical information to a reasonable conclusion based on individual patient data. Part II then applies that approach to understanding disease mechanisms, and concludes that arterial constriction, caused largely by sympathetic activation under the influence of stress, is likely to be an important initiating factor in many cardiovascular diseases, particularly heart attack and stroke. I go on to look at the possible role of such vasoconstriction in other disease. Part III suggests that arterial constriction may even be important in cancer pathogenesis and evolutionary mechanisms, through ischemic (blood flow reduction) destabilisation of a genome composed essentially of naturally genetically-engineered viral modules. The important conclusion then is that evolution is perhaps best seen as natural genetic engineering.
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Preface

Preface to the First Edition

I profess neither genius nor expertise in matters philosophical, but I believe I have developed a view worth communicating about ways of analysing evidence in Medicine and synthesising it to best conclusions. With it, I am persuaded that when applied to the vast and increasing mass of data in medical science, such an approach can lead to an improved understanding of a range of human disease mechanisms. This book is written to convey and illustrate this view.

Essentially my views have stemmed from two sources of disquiet. The first is the way in which the almost geometric progression of data in many fields of medical science seems to have totally outstripped our capacity to interpret it. It may or may not be true that each sub-specialist area of medicine, be it biochemistry, physiology or pathology, does have adequate means of interpreting its own data, but when we come to the general synthesis of data overall in any field, current concepts seem to me hopelessly inadequate. In some areas, of course, more data will be needed before we can draw any final conclusions; but even in fields where we already have a good body of evidence, our present concepts are often not very sophisticated, and not always the best possible. Unless we can begin to formulate some generally agreed upon interim conclusions, and methods of reaching them, the continued rapid expansion of the data may eventually completely overwhelm our capacity to assimilate and interpret it, and the opportunity for making unified syntheses may then be totally lost.

I am uneasy about the views of many philosophers of science, in particular Karl Popper\textsuperscript{1} which assert that the process of creating a hypothesis is beyond the realm of logic, and therefore beyond our capacity to analyse. The approach I shall be developing in this monograph contradicts this view. In my view, hypotheses should not be mere figments of our isolated imaginings, but syntheses based on the very data itself. How to formulate a "good" hypothesis, or at least a good "working" hypothesis, then becomes a matter of how to synthesise the data to its simplest and at the same time most rational conclusions, based on the broadest body of evidence available at the time. This is the essential concern of the initial chapters of this monograph. Essentially, what I will be suggesting is that we should initially analyse the evidence within separate but interrelated subgroups, and draw initial sub-conclusions within each, before going on to higher levels of hierarchic resolution of the problem as a whole.

Having established some ground rules relevant to that initial approach of simplification, Part II then goes on to illustrate the way novel conclusions can be developed as useful working hypotheses over a broad range of diseases. Following this, and as common threads begin to emerge from many diverse areas, a unified theory is developed relating stress and arterial vasospasm to much human disease.

All this may sound like heady stuff, but essentially my intention is merely to bring hypothesis-formulation out of the arena of idle imaginings and armchair speculation, and back to where it belongs, namely in the realm of data analysis, interpretation and synthesis. The essence of this approach is simplicity. It is only by simplifying the process of data analysis that the average mind can even begin to grapple with the enormous bulk of evidence bearing on the various disease states within medicine, spanning as they all do the whole breadth of so many different specialist areas of medical science.

I recognise that the idea that we can synthesise data to rational conclusions contains more than a "whiff of inductivism"\textsuperscript{2} but I make no apologies for that, for I believe that the modern-day rejection of induction as a valid process has been carried too. And I am not alone in this thought.\textsuperscript{2} The general approach suggested in Part I for data analysis and synthesis in medicine is simple, but, in its separate parts, much of it is not new. The approach merely allows us to see things differently and I offer it in the hope that others might find in it of some value. I have no doubt that there will be many who disagree, both with the general approach itself and the conclusions derived from it. Others will see much of it as common sense, and in one respect that judgement would please me more than unqualified agreement. If we could take common
sense out of the realm of wisdom with hindsight, and make it work for us in a more prospective or predictive way, we should have gained much more than an ability to understand a few points about a few medical diseases. In that respect this book is, as much as anything else, about the nature of common sense or, as I prefer to call it, 'bush logic'. Such comprehension lies, in my belief, at the very heart of the process of creative discovery.

Whether I can make any inroads into common sense or not, the words of Ackoff certainly have the ring of truth when applied to the current usage of that term:

"Common sense . . . has the very curious property of being more correct retrospectively than prospectively. It seems to me that one of the principal criteria to be applied to successful science is that its results are almost always obvious retrospectively; unfortunately they seldom are prospectively. Common sense provides a kind of ultimate validation after science has completed its work; it seldom anticipates what science is going to discover." 3

Part 111 of the book, explores the ground beyond mere interpretation in an attempt to gain an improved understanding of some of the most obscure areas of medical science, including the nature of cancer and evolution. However, I would stress that its foundations remain based within the data, and even where it goes beyond, it still tries to keep within the bounds of the reasonable by drawing on such tangible supports as models and analogies borrowed from other fields of experience. Although the data tackled are often difficult, the basic approach remains in essence simple, and certainly no deep philosophical models are involved. Indeed, the approach facilitates the further drawing together of common basic overall threads at the end of the book to allow me to put forward a unified theory linking stress, disease, and evolution. The book ends by returning again to its central theme, namely how we might proceed to achieve a better understanding of disease mechanisms within the always-limited frameworks of existing data.

Because I shall be taking a broad look at a number of diverse disease areas, the reader is entitled to know something about my background, to better judge where I speak with some expertise and established research experience, and wherein I am reliant more on my general experience, my reading, my methods, and in the last analysis, my imagination.

I was brought up in Sea Lake, in the outback of North-Western Victoria, Australia, and completed a combined degree in science and medicine at the University of Melbourne, graduating B.Sc. in 1955 and MB.BS in 1958. It was from these two very different general backgrounds that I first began to sense the presence of fundamental differences between the problem-solving ways of the practical world and those taught from within the academic one, and moreover to perceive that the latter were not necessarily more accurate, and certainly not usually more efficient! After completing my postgraduate clinical training at the Royal Melbourne Hospital and gaining my M.D. and FRACP in 1962, I went to the Howard Florey Laboratories of Experimental Physiology and Medicine to work towards a Ph.D. (awarded 1969) under Prof. R.D. Wright in collaboration with D.A. Denton and colleagues. The subject of my thesis was "The role of body fluid volumes in the control of aldosterone secretion in the conscious sheep". This led me to an interest in the physiology of the renin-angiotensin system and through that, to the general research area which has been my field since, namely the pathogenesis of hypertension.

In 1965 I went to work with W.S. Peart at St. Mary's Hospital, London under the sponsorship of the Nuffield Foundation, intending to stay for a year. In the event I stayed for nine, first as a Research Fellow and subsequently as Senior Lecturer in Medicine at St. Mary's. During those years my research interest focused on the nature of renal hypertension, where Peart and I, together with our collaborators, were able to contribute to the understanding of the role played by the renin-angiotensin system by developing angiotensin antibodies both to measure circulating angiotensin II and plasma renin activity, 4-6 and to use as specific pharmacological blockers of the renin-angiotensin system in experimental renal hypertensive animals. With these and other methods we established that the renin-angiotensin system could not alone account for chronic renal hypertension. 7,8 Because of this I proceeded to investigate
renal extracts for other pressor materials. In the event, I found no new non-renin material, but did discover a high molecular weight form of hog renin which I subsequently characterised.

In 1977 I took up the Chair of Medicine at the University of Tasmania in Hobart. In this position, I soon began to see the necessity for taking a broader view of disease than I had done previously when fascinated by research within the sub-speciality area of hypertension. I felt a need to be in a position to analyse what my colleagues in different clinical areas were saying so that I could comment sensibly upon their views, and a desire to formulate a logical basis from which our introductory undergraduate clinical students might begin to build clinical diagnoses of their own, given that their background at that stage would be solely in the preclinical disciplines of anatomy, physiology and general pathology etc. These two different stimuli led to an initial rough method of clinical problem-solving which I found useful, and not only in teaching clinical method, but also in the diagnosis in difficult patients of my own. Moreover, as I refined the approach, I found that the more I applied it to individual patient-diagnosis, the more I was led to question traditional views about the pathogenesis of a whole range of clinical disorders. This, therefore, was the starting point for a somewhat different approach to understanding of disease mechanisms, and it was from these beginnings that this monograph eventually stemmed.

It will become obvious that most of the areas I shall deal with in this book are remote from my immediate areas of expertise, particularly where I discuss the nature of auto-immunity, cancer, evolution, and the philosophy of science. Because of that I should say that I have attempted, as far as possible, to fill the gaps in my knowledge by reading widely before putting pen to paper. Gaps, I am sure, still exist, but I hope to have kept these to a minimum, and at worst to have avoided major errors of knowledge and interpretation. Given this, I trust that the reader will not be too troubled by any lesser errors, since in these days of ultra-specialisation anyone undertaking a task as broad as this is unlikely to be correct at all levels of detail. Rather, I would prefer to be judged on my general approach and the way I have applied it, for if I have this right, the conclusions themselves should not be too far off the mark. Whatever the case, I do not seek unqualified agreement with my views, but wish to provoke those who disagree with them to show wherein my process of interpretation has been wrong. The more of that sort of criticism the better, certainly far better than the deafening silence which is indifference.

In the final analysis it will always be the experimental data itself which establishes the truth or falsity of propositions in medical science, but unless we can begin to formulate concepts somewhere along the way towards being right, the really crucial experiments may never be performed. In that case, the act of discovery will largely be a matter of luck, and I believe we can do better than that.

The views I will develop in this monograph about the relationship between stress, arterial vasoconstriction and disease have been published in outline previously, first as my Inaugural lecture to the University of Tasmania and subsequently elsewhere in the medical literature.

Finally, I wish to acknowledge my gratitude to Mrs. S. Petrie for her secretarial assistance; to the staff of the University of Tasmania Biomedical and Clinical Libraries for their unremitting help in providing reference material; to my many colleagues in the University of Tasmania, Clinical School and Royal Hobart Hospital, especially Dr. A.J. Galbraith, Dr. M. Denton and Prof. J. Reid, for their stimulating contributions towards our many discussions; and finally to my wife and family for their tolerance of the apparent eccentricity of this endeavour.

G. W.B. 1983

Addendum

The above was written in July 1983, when the whole of the manuscript of this book had also been completed. Unfortunately, at that stage, prior commitments for publication were withdrawn because of publishing house failure, and several years then elapsed before suitable
alternative arrangements could be made. In that respect, I am indebted to the University of Tasmania for the final production of the first edition of this book.  

Because of the passage of those years between original writing and final publication, much data bearing on the book's various aspects have since accumulated, particularly in relation to earlier-written chapters. Two comments therefore. First, I have updated each chapter with relevant additional text and references where necessary. Second, it is surprising how little that accumulated data has actually changed the concepts of the original manuscript. True, it has often determined a change of emphasis, but the fundamental hypotheses have not been basically altered. And allowing for the vast accumulation of information on each topic every year, that seems to me to go at least some way towards vindicating the views put. I shall now leave this for the reader to judge.

G.W.B.  
Sept 1989

Preface to the 2nd (eprint) edition. 2012

This manuscript is now to be posted on the University of Tasmania eprint website at:

http://eprints.utas.edu.au/12671/

I have revised the first edition before placing it on this eprint site. The general tenet of the thesis is, to me, as reasonable as ever.

G.W.B 15th Nov 2012

References


