

## GIUSEPPE MORUZZI LECTURE

# THE BASIC IMPORTANCE OF THE PHYSIOLOGICAL APPROACH IN CLINICAL MEDICINE: THE EXPERIENCE IN THE AREA OF HYPERTENSION

A. ZANCHETTI

*Centro Interuniversitario di Fisiologia Clinica e Ipertensione, Università di Milano, Ospedale Maggiore,  
and Istituto Auxologico Italiano, Milano, Italy*

### INTRODUCTION

It is not without emotion that I have accepted to give a lecture named after my first teacher, Professor Giuseppe Moruzzi. From him I have learned most of what I know of scientific methodology. From him I learned the ethical approach to research, i.e. research for understanding rather than for confirming our own cherished hypothesis, a value that has got lost in the current witch-hunting for financial conflicts of interest, while the major conflict of interest – as Giuseppe Moruzzi taught us – is with our own scientific prejudices, our preconceived ideas, our striving for publication, impact factor and career.

Giving a lecture named after Giuseppe Moruzzi gives me the opportunity of going back to my own research sources: in research, too, “home is where one comes from”. Therefore I have accepted with enthusiasm the suggestion of my colleagues of the Department of Physiology and Biochemistry of the University of Pisa to discuss the impact that the physiological approach has had in hypertension research and clinical hypertension. I apologize if, in doing this, I shall be too appreciative of the approach that has characterized my research career.

When I started as a medical student and junior investigator under the guidance of Giuseppe Moruzzi and Cesare Bartorelli, about 50 years ago, first in Parma, then here in Pisa and finally in Siena, our understanding of arterial hypertension was very scanty and our therapeutic abilities close to nothing. It was even ignored whether hypertension was a mechanism of disease or a compensatory mechanism not to be interfered with. As late as 1957, an article in an authoritative journal such as the *Lancet* could plainly state “Even in the case of true arterial hypertension ... neither product of test-tube or crucible halts, nor delays materially, the unfavourable course of the disease”. In order to have a measure of what has been achieved, in the last 50 years, this conceptual and therapeutic nihilism should be contrasted with what is written in the most recent guidelines on the management of arterial hypertension, those jointly prepared by the

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Correspondence to: Prof. Alberto Zanchetti, Centro Interuniversitario di Fisiologia Clinica e Ipertensione, Via F. Sforza 35, 20123 Milano, Italy

European Society of Hypertension and the European Society of Cardiology (1): "On the basis of current evidence, it can be recommended that blood pressure, both systolic and diastolic, be intensively lowered at least below 140/90 mmHg and to definitely lower values, if tolerated, in all hypertensive patients, and below 130/80 mmHg in diabetics".

#### SUCCESS OF THE PHYSIOLOGICAL APPROACH IN THE DEVELOPMENT OF EFFECTIVE ANTIHYPERTENSIVE TREATMENT

I first became acquainted with arterial hypertension, when helping - as a medical student can help- my teacher Cesare Bartorelli, who was preparing an extensive review on essential hypertension to be presented at the annual congress of the Italian Society of Internal Medicine in 1950 (2). The therapeutic approach to hypertension was then, as remarked above, close to nothing: the two most popular approaches were surgical thoraco-lumbar sympathectomy and Kempner's rice diet. I still remember George Pickering telling of his visit several years earlier to Kempner's clinic, that he compared to a Nazi concentration camp. Even the severe hypertension of a personality such as that of the USA president Franklin Delano Roosevelt could not find any suitable treatment, and ended in a fatal stroke in 1945 (3).

However, by 1950 a considerable body of physiological knowledge had accumulated about various mechanisms of blood pressure control: 1) the sympathetic nervous system, its regulation by baroreflexes, its neurotransmitters, with von Euler's identification of noradrenaline and its differentiation from adrenaline dating 1948; 2) research on the renin-angiotensin system was still in its early stage, but the seminal experiment by Goldblatt had opened a new path of physiological and biochemical investigation; 3) the kidney had also been in the focus of interest, thanks to the brilliant pathophysiological work of Franz Volhard.

It is no surprise, therefore, that the first drugs that were developed during the 1950s and found effective in lowering blood pressure were agents interfering with the sympathetic nervous system, i.e. ganglionic blocking drugs, antiadrenergic agents such as guanethidine and brethylum, and reserpine. By using ganglionic blockers and antiadrenergic compounds, though they carried plenty of severe adverse effects, it was possible to demonstrate that the extremely high 5-year mortality of malignant and severe hypertensives could be dramatically reduced from 99%, to less than 50% (4). Subsequent progress in the physiological knowledge on sympathetic nervous system organization brought to the development and therapeutic use of selective antagonists of  $\alpha$ - and  $\beta$ -adrenergic receptors (and subtypes of these receptors) and to agents active on central mechanisms of blood pressure regulation, such as  $\alpha_2$ -adrenergic receptor agonists and imidazoline- $I_1$  receptor stimulants. It is interesting that development of these agents also helped to further clarify the physiological organization of central neural blood pressure control mechanisms.

Likewise, it was the detailed knowledge of the physiology of ion transport across the renal tubules that led to the development of orally active diuretics, the thiazides,

that first made treatment of milder forms of hypertension effective and tolerable. The same virtuous cycle of physiological knowledge prompting the development of new classes of antihypertensive agents or explaining their mechanism of action, and of the new agents then becoming investigative tools for physiology, can be seen for the development and therapeutic success of calcium antagonists, the inhibitors of angiotensin converting enzyme and the angiotensin receptor ( $AT_1$ ) antagonists (5).

#### THE PHYSIOLOGICAL APPROACH IN THE UNDERSTANDING OF THE MECHANISMS OF HYPERTENSION

Independently of the transduction of physiological research into successful treatment of hypertension, progress in the understanding of hypertension has developed in the second half of the twentieth century thanks to close interaction between physiological research in experimental animals and man (6). I shall give a few examples from my own investigations and those of my associates, not because I presume these were the most important ones (essential contributions have come from many research groups throughout the world), but in order to add a bit of personal experience to this overview.

An area of research in which our group has been particularly active has been the investigation of the sympathetic control of circulation in hypertension (7, 8). Methods were developed for selective stimulation and deactivation of carotid sinus baroreflexes by a neck chamber, enabling us to describe the resetting of these reflexes in human hypertension and the effects thereon of several types of antihypertensive agents. Selective deactivation of cardiopulmonary reflexes could also be effected by a lower body low pressure chamber, and the demonstration given of the resetting of these reflexes accompanying left ventricular hypertrophy. Sympathetic neuronography from the peroneal nerve has provided evidence of increased sympathetic activity in selective groups of hypertensives, particularly the most severe and the obese.

Another topic in which we have been particularly active is that of the interactions between the sympathetic system and the kidney in cardiovascular regulation. By using the experimental model of comparing function in an innervated and the contralateral denervated kidney, we were able to demonstrate that sympathetic renal nerves not only induce renal vasoconstriction, but stimulate antidiuresis and renin release, that the sympathetically mediated renin release is mediated by  $\beta$ -adrenergic receptors, that diuretic-induced renin release can be independent of direct renal effects and is largely mediated by the renal nerves, and that there are reno-renal reflexes inhibiting contralateral sodium reabsorption and renin release (9, 10). The positive feedback nature of most of the sympathetic-renal interactions suggests they may participate in the pathogenesis of arterial hypertension, both when the initiating factor is neural and when it is renal (11). On a practical point of view, evidence of these positive interactions represents a suitable background for the current suggestion of a widespread use of combination therapy in hypertension, because hypertension and its complications are more likely to be reduced by interfering with more than a single mechanism of blood pressure control (1).

## IS THE PHYSIOLOGICAL APPROACH CHALLENGED BY NEW APPROACHES TO RESEARCH?

We are all aware that the supremacy of the physiological approach to clinical medicine is being endangered by the rising of two new approaches, namely molecular and genetic medicine and large randomised therapeutic trials. Needless to say, both are extremely important new tools in medical research to be encouraged and considered with expectation. However, they should not be considered, as some of their worshippers do, as the ultimate advance promising the only real conclusions and unforeseen progress: "le magnifiche sorti e progressive" of medical research.

There is no doubt that molecular biology provides a much deeper insight into physiological mechanisms: structures until recently purely hypothetical such as adrenergic or angiotensin receptors can now be precisely identified and even cloned (although cloning a receptor does not necessarily mean that receptor is physiologically relevant). There is an increasing need of closer and closer collaboration between different physiological approaches: more minute is the reality being explored and more detailed the type of information we are able to obtain, greater is the need of an integrative approach. The surge of genetic research has also had important reflections on hypertension research, and a few rare forms of monogenic hypertension, such as Liddle's syndrome, glucocorticoid-remediable hypertension, the syndrome of apparent mineralocorticoid excess, have had their genetic mechanisms clarified (12). Unfortunately, essential hypertension is, as most of the widespread diseases, a polygenic condition, and the identification of the multiple genes responsible for the complex inheritance of blood pressure has proven elusive. As underlined in a recent editorial on the *Journal of Hypertension*, "genetic association studies of complex disorders are often characterized by underpowered studies, in addition to a lack of sound evidence for the proposed candidate genes ... Positive findings should be followed by both genetic replication studies and *physiological research into the mechanisms involved. The latter requirement is lacking in many instances ...* (13)". This very reasonable recommendation, physiology should precede and follow genetic analysis, is too often forgotten in the enthusiasm of many investigators, and the mass media amplification of such an enthusiasm unfortunately results in directing funds away from any other research approach. The last European Union program for medical research was almost entirely directed to genetic investigations.

The other danger to the physiological approach to clinical medicine comes from uncritical enthusiasm for the large randomized therapeutic trials. They are often arrogantly defined as "evidence-based medicine" (14), as if they were the only studies to provide real "evidence". I do not want to be misunderstood, I believe randomized trials have become an important tool in medical research, and hypertension experts can be proud to have been the first to use them to test the benefits of a cardiovascular therapy. The real problem is not whether medicine should be based on evidence, but which are the types of evidence upon which it should be based. A few years ago, in an editorial on the matter, we commented: "Placing clinical trials at the top of a scale of scientific importance and dignity can not only be illogical, but also dangerous for science

itself. Consideration of how medical progress was achieved in the past indicates that the understanding of the mechanisms of a disease has always been the key to this progress ... Any undue claim of superiority of randomised clinical trials over previous steps may only contribute to create an imbalance of research activity and funding that can ultimately threaten the very background on which trials themselves are planned and conducted (15)". This view was fortunately shared by the committee that prepared the 2003 European Society of Hypertension – European Society of Cardiology guidelines for the management of hypertension, that stated "the Committee members take the view that, although large randomised controlled trials and meta-analyses provide the strongest evidence about several aspects of therapy, scientific evidence is drawn from many sources, and when necessary all sources have been used" (1).

The worshippers of "evidence-based medicine" use to contrast the figures of Claude Bernard and Pierre Louis in French medicine of the 19<sup>th</sup> century, the deterministic experimental method of the former to the statistical approach of the latter. Pierre Louis has the undoubted merit to have definitely shown the lack of benefits and indeed the dangers of the practice of bleeding. His achievement is, at the same time, the demonstration that evidence-based medicine most often comes to give the final touch of proof to what other considerations, or other types of evidence, have already shown: the practice of bleeding should have been discredited long before Pierre Louis' time, if Moliere's *Malade Imaginaire* listed "Clysterium donare, Postea seignare, Ensuita purgare" in the *pontus asinorum*, the sea of the donkeys.

In conclusion, trials are important as a later or conclusive step to confirm the benefits of an intervention, but physiological research is the only one opening new ways, clarifying new mechanisms, suggesting new therapies or interventions.

## SUMMARY

Since Claude Bernard the physiological approach has dramatically contributed to the unprecedented progress that clinical medicine has seen during the second half of the 19<sup>th</sup> and throughout the 20<sup>th</sup> century. If I go back to about fifty years ago, when I started as a medical student and investigator under the guidance of Giuseppe Moruzzi and Cesare Bartorelli our understanding of arterial hypertension was very small and our therapeutic abilities close to nothing, but progressive knowledge of the physiology of the sympathetic nervous system, of the kidney, of the renin-angiotensin system, etc, led to a progressive understanding of the mechanisms of elevated blood pressure and to the development of an array of effective blood pressure lowering drugs, thanks to which hypertension is now a controllable disease.

The supremacy of the physiological approach to clinical medicine has been recently endangered by the rising of two new approaches, whose worshippers consider the ultimate ones promising solid conclusions and unforeseen progress. These are the large randomized therapeutics trials, that are often arrogantly defined as evidence-based medicine (as if they were to provide the only real "evidence") and molecular and genetic medicine. Needless to say, both are important new tools in med-

icine, but neither can make the physiological method obsolete. The risk of the pretended superiority of the new approaches (and the new fashions) is that these claims are unbalancing research activity and its financial support, thus weakening the very basis upon which these new methodologies are founded and have developed.

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