CHEMISTRY

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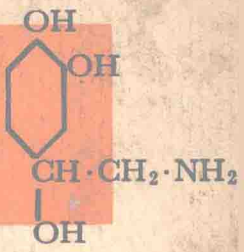
PHARMACOLOGY

CLINICAL ASPECT

NORADRENALINE



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An attempt is made to give a fairly comprehensive series of data concerning noradrenaline in its functions as the SYMPATHETIC NEUROHORMONE and as a SUPRARENAL MEDULLARY HORMONE, together with some implications as to its use as a therapeutic agent.

The OCCURRENCE, PROPERTIES, and ACTIONS of noradrenaline have been treated in a series of chapters, including a brief historical review. In general, the chemistry, physiology, pharmacology, and clinical applications have been subject of treatment. Methods for its estimation are presented in detail.

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NORADRENALINE

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CHEMISTRY, PHYSIOLOGY, PHARMACOLOGY AND CLINICAL ASPECTS

By

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TO
SIR HENRY DALE

PREFACE

The rapid development of the concept of NA as adrenergic nerve transmitter and suprarenal medullary hormone since 1946–1947 as well as its growing therapeutical applications have made it desirable to bring the scattered data together in a volume. A complete literary survey of the subject has not been attempted but it is hoped that most of the earlier work has been considered. Of the many publications available after the completion of the manuscript in April, 1954, some have been included as addenda.

The author expresses his thanks to several colleagues who kindly have placed unpublished material at his disposal and also to Journals and Publishing Houses for the permission to use illustrations and other material. Separate acknowledgment is made to the authors and journals in the legends to each illustration.

The volume is dedicated to Sir Henry H. Dale in whose laboratory I had the privilege to work in 1930 and 1937. I am profoundly indebted to him not only for writing the introduction, but also for revising most of the manuscript and for many valuable suggestions. It is also a pleasure for me to thank Professor H. Theorell of the Nobel Institute for Biochemistry who kindly read Chapters II and III. My thanks are also due to Miss D. Cronstedt for her patient and careful work in preparation of the bibliography and other material.

U.S.v.E.

Stockholm, Sweden
May, 1955

INTRODUCTION

By

Sir Henry H. Dale, O.M., G.B.E., F.R.C.P., F.R.S.

Nor-adrenaline—nor-epinephrine, amino-ethanol-catechol, adrenaline's primary amino-homologue—though it has been known as a chemical curiosity since Stolz made it by artificial synthesis in 1904, more than half a century ago, has leaped to fame and become almost suddenly a center of interest to a wide circle of investigators in many countries, since P. Holtz in Germany and U. von Euler in Sweden, as recently as 1946, separately and almost simultaneously recognized its presence in the animal body, as a natural constituent. The bibliography which Professor von Euler has assembled at the end of this valuable monograph, contains some 750 references to publications, of which the very large majority have therefore appeared from 1946 onwards–in a period of less than nine years, and nearly all of these deal with nor-adrenaline, or with points of interest bearing upon its occurrence in the body, the methods of recognizing it and of measuring the amount of it present in an extract and of separating it from other constituents, its natural origin and fate, its pharmacological actions and its physiological significance, and with everything, in fact, which has now been put upon scientific record with regard to its nature, occurrence and function. There can seldom have been a case in which a substance, with no more than a restricted claim to special importance for therapeutics, or for any other practical application, has attained so rapid a

celebrity, or has given rise, in so short a period, to so large a volume of research by so many experienced investigators. The interest which it has thus attracted is due, of course, not merely to the discovery of its natural occurrence, but largely to the implication, and the eventual endorsement of this by direct evidence, of its important functions in the animal body, and especially of its action as the predominant chemical transmitter of the effects of adrenergic nerve impulses, mainly in postganglionic sympathetic nerve fibres, to the effector cells in contact with which such fibres end. Hardly less interesting is the evidence, now available, for the presence of nor-adrenaline together with its methylamino-homologue, adrenaline, as a component of the sympathomimetic hormone of the suprarenal medulla, and for its consequent presence, till recently unsuspected, in the preparations of natural adrenaline from animal suprarenal glands, which have so long been available for therapeutic uses.

Interesting, again, is the similarly new evidence for the occurrence of nor-adrenaline as the predominant sympathomimetic constituent in foetal chromaffin organs, and in pathological tumours of the adrenal medullary tissue, and for its possible function as the penultimate stage in the vital synthesis of adrenaline in the suprarenal glands.

All this recent burst of discovery has had a more than ordinary interest for me, on account of the link which it presents with some very early and indecisive observations of my own, to which Professor von Euler has been good enough to make reference. About 1909–10 I was exploring, with the chemical co-operation of my late colleague, George Barger, the way in which, in a series of amines which approximated in structure by successive stages to that of adrenaline itself, the activity to which I then first referred as "sympathomimetic" appeared and grew stronger

and more closely specific as the structure of adrenaline was approached. The nearest relative to adrenaline then readily available was its artificial, primary homologue, dl-nor-adrenaline (arterenol), and I had no difficulty in confirming the earlier findings of other observers that this substance usually, though, according to my experience not quite constantly, showed a vasopressor activity–the most familiar and most frequently measured of the sympathomimetic effects – somewhat more powerful than that of the homologous dl-adrenaline. For me, however, it had a much greater interest, as being a member of one of several series of catechol derivatives, with various and differently animated side-chains, in which I had found that the actions of methylamino-members of each series reproduced several of the inhibitory sympathetic effects much more powerfully, in relation to the augmentor effects, than did those of its primary amino-homologue. To this rule nor-adrenaline was no exception; and I was impressed by the fact that this relatively weaker production, by nor-adrenaline, of most of the inhibitor components of the actions of adrenaline, made it in fact and to a significant degree, more accurately sympathomimetic in the details of its action, even than adrenaline itself. I find it curious, even a little humiliating, to reflect that the main significance which I found in this observation at that time, was that it seemed to make it difficult to accept the brilliant hypothesis which had been put forward some five years earlier by my friend, T. R. Elliott, attributing to adrenaline the function of a chemical transmitter of the effects of sympathetic-nerve impulses. It seems now so obvious, in the light of all that has happened since Otto Loewi produced the first direct evidence for such a function in 1921, that we ought to have recognized immediately the possibility that Elliott's hypothesis might still be right in principle, and that the next step should have

been to test, even in 1910, the possibility that the suprarenal hormone, and, if then only by implication, the suggested sympathetic transmitter, might contain nor-adrenaline as well as adrenaline, and that the former might even, at many nerve-endings, be the predominant component of the transmitter. I am tempted to speculate whether, if such a possibility had been envisaged thus early, another friend of mine, the late W. B. Cannon, might not have recognized nor-adrenaline as an obvious candidate for the rôle of his "Sympathin E." It now appears to me, in any case, that the much more recent, and brilliantly successful, direct demonstrations of the natural occurrence and the transmitter function of nor-adrenaline, has made the hypothesis of the ambivalent transmitter "sympathin," and its E and I combinations with the corresponding receptor substances, no longer necessary. It served its purpose well, as the stimulus for a whole series of distinguished investigations, some of which have given results of great suggestive value, even for the more recent and detailed assessment of the contribution of nor-adrenaline to the sympathetic transmitter function. It may be doubted, however, whether the theory is likely now to retain even this suggestive value; and I am inclined to share also the doubt expressed by Professor von Euler in this monograph, whether the continued use of Cannon's term "sympathin," in view of its former association with his special theory and its rather ambiguous application, would not tend now to confuse rather than clarify ideas.

A further question, which obviously might now arise, is whether other homologues of the adrenaline series are likely to be found, occurring naturally in the animal body, and contributing to either the hormonal or the transmitter functions of those already identified. I am not aware of any evidence to suggest the natural presence or functional

participation of the next higher, ethylamino-homologue; but, from what has been observed of its action, qualitatively similar to, but quantitatively weaker than, that of nor-adrenaline, it may be doubted whether its occurrence in a minor proportion would be recognized; while, on the other hand, its presence as a major component is unlikely to have escaped detection with the methods now available. The position is rather different with regard to the next upward step in the series, the isopropylamino-homologue. This has been known for some years, and has been produced, synthetically, for therapeutic application, on account of an activity in which the inhibitory components of the actions of adrenaline are so accentuated as to predominate. Dr. Mary Lockett has more recently produced suggestive evidence for the presence of this isopropyl-nor-adrenaline in extracts from the suprarenal glands; and the possibility of its making a minor contribution to the transmission of effects from some adrenergic nerve-endings obviously remains open, though its experimental demonstration might remain for long, if not for ever, impracticable.

It is obvious that this recent, remarkably rapid advance in our knowledge of nor-adrenaline and of its physiological significance, has been greatly facilitated by the relatively new physico-chemical methods, such as counter-current solvent distribution and paper-chromatography, which have now become available for the separation of very small quantities of sensitive and closely similar substances. Even with all such aids, however, the opening and rapid development of this new chapter, giving the long hidden meaning of an old story, seems to me to reflect the greatest credit on all who have contributed to a courageous and skillful enterprise, with results which are so convincing. It is a matter for great satisfaction that one of the pioneers of this new phase Professor von Euler, should now have undertaken

the heavy labor of collecting, and bringing under expert review, all the mass of evidence, most of it so recently made available, about nor-adrenaline, and about the details of the many methods of research, including again some comparative novelties, which have contributed to this new recognition of its importance and its interest. His monograph gives the story in every accessible detail, and brings it fully up to date. It will be indispensible to anybody working in this field, and it offers a wealth of information to a much wider range of those, who are interested in following the progress of physiology and pharmacology at one of the points at which these are in process of rapid growth.

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