BIOCHEMICAL NEUROLOGY

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Preface

'... it is probable that by the aid of chemistry many derangements of the brain and mind, which are at present obscure, will become accurately definable.'

J. L. W. Thudichum (1884) *Chemical Constitution of the Brain.*

Dysfunction of the human nervous system may be interpreted at different levels of the system's own organizational complexity. For centuries neurological disorders had to be assessed mainly by means of the unaided human senses. In the present century, light and electron microscopy have opened the way to an understanding of neurological disorder at a cellular and subcellular level, while electronic amplification devices have permitted the study of nervous system dysfunction at an electrophysiological level. In recent years there has been increasing investigation of both normal and abnormal neural function at its ultimate level, the molecular or chemical one. In the last analysis, all dysfunction of the nervous system must somewhere involve alterations in its component molecules. At present it is not possible to provide a complete account of all molecular changes which must occur in the various neurological diseases. However, biochemical knowledge of neurological disorders has grown rapidly and sufficient material is now available for a moderately coherent biochemical interpretation of many neurological diseases. In the past, when neurological disorder could be explained at a molecular level, the material has often been presented as if the main aim was to illuminate normal neural function. In the present work, the subject of biochemical neurology is presented with the main aim of interpreting in molecular terms, as far as seems possible, the disorders which comprise the content of clinical neurological practice. This approach may lead to a result which may appear unbalanced to the scientific neurochemist, but it may prove more relevant and useful to the clinical neurologist. The latter, looking at familiar clinical facts from a relatively unfamiliar biochemical viewpoint, may gain new insights and become aware of gaps in neurochemical knowledge. Thus research may be stimulated. A chemically-based approach to clinical neurology should include the study of neuromuscular as well as purely neural diseases. Muscle disease is customarily regarded as part of the field of clinical neurology, though there are some major chemical differences between neural and muscular tissue.

To what extent can the content of contemporary clinical neurology be regarded as biochemical? All neural and neuromuscular disorders ultimately involve molecular changes, and all genetic disorders are determined by abnormalities of desoxyribosenucleic acids. Therefore it might be argued that the scope of biochemical neurology includes all clinical neurology. However, any attempt at present to deal with all neurological disorders at a biochemical level would show substantial areas for which little biochemical information is available. This book therefore deals only with those neurological conditions where contemporary biochemical knowledge contributes significantly to their understanding. Where the relation between a disorder and a described biochemical abnormality appears too tenuous, e.g. the question of altered central cholinergic neurotransmission in Alzheimer's disease, we have generally felt it inappropriate to discuss the matter, bearing in mind the level at which the book is written. We have also omitted from consideration disorders in which described biochemical abnormalities appear to be purely consequences of a disease process which itself has no known biochemical basis or mechanism. Because of this policy we do not discuss a disorder such as subarachnoid haemorrhage, even though this may lead to clinical biochemical abnormalities, e.g. glycosuria.

Thus we have attempted to write a book interpreting dysfunction of neural and neuromuscular tissues at the molecular level, directed towards the interests of those who investigate and treat such disorders clinically, be they neurologists, physicians, paediatricians, psychiatrists or pathologists. Such an approach may also be of value to laboratory-based neurochemists and biochemists, despite its obvious shortcomings from their point of view.

Throughout the book references have not been supplied to material widely available in standard texts on biochemistry and clinical neurology. Except for recently published work unlikely to have yet been included in the review-type literature, we have preferred to cite reviews of subjects or papers with extensive bibliographies, rather than original research contributions. Thus it is hoped that the reader will be provided with an entry to the relevant literature, without the text becoming unduly cluttered with references.

We are indebted to many persons for help in preparing this book and in particular would wish to express our gratitude to Mrs Janet Wickham for patiently transforming so many pages of largely indecipherable handwriting into a highly professional typescript, to Mr D. Sheehy for drawing the numerous chemical formulae and other illustrations, and to Mr G. Jurott for photographing them. We would also wish to indicate our thanks to Dr J. Marks, of Girton College, Cambridge, for instigating this project, and to Mr D. Bloomer of MTP Press, for his encouragement and help throughout its course.

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May, 1982

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The arrangement of the material

In writing for clinicians, it is difficult to know how much biochemical detail to present, and what basic knowledge of chemistry to assume. Generally in this book we have tried to give only enough chemistry to show the reader the structures of the various molecules considered and to follow the different chemical reaction sequences discussed. Reaction mechanisms as such have not been considered. Illustration devices such as shading have been used to allow the reader's eye to follow the fates of relevant portions of molecules more easily, and to emphasize aspects of molecular structure which are pertinent in particular contexts. We have assumed relatively little background chemical knowledge on the part of the reader, though we realize this policy may irritate those chemically more sophisticated. For simplicity we have often not followed all the ramifications of a particular chemical reaction at the one time, but have concentrated on those aspects germane to the disturbance currently under discussion. However, we have attempted by cross-referencing to bring out the interrelations between the various reactions of the one molecule which can yield different chemical products and be responsible for different diseases. Thus it is hoped that material presented as individual chemical facets can later be synthesized by the reader into a biochemical overview.

The material has been arranged around a concept of biochemical functioning of nervous tissue in a way which it is hoped may be relevant to the clinician, but which may appear unconventional and perhaps inappropriate to the biochemist. We have tried to fit the individual biochemical neurological disorders into this arrangement, even when the fit has sometimes not been a particularly comfortable one, because we wished to present the individual disturbances in relation to an over-riding concept of neurochemical function, rather than describing the disorders as a series of self-contained and sometimes apparently unrelated chemical entities.

1.1 THE APPROACH TO THE SUBJECT

It seemed possible to deal with biochemical neurology in two main ways. First,

we could follow the conventional biochemist's method of considering in turn the various classes of molecule found in neural tissue and muscle, and then discuss the neurological disorders associated with disturbed metabolism of each of these classes of molecule. Secondly, we could take the various diseases in the order in which they are dealt with in most textbooks of clinical neurology, and describe the abnormal chemistry of each condition in turn. The latter approach had the advantage that the book's intended reader, the clinician, would move from the more familiar to the less familiar. He would see the chemistry in relation to clinical data that he already knew. Unfortunately, however, it would mean that chemically unrelated conditions might be dealt with side by side, and chemically related conditions might be divorced. It would therefore be more difficult to develop any comprehensive view of normal and abnormal neurochemistry, unless what might appear to the clinician as an indigestible and doubtfully relevant body of normal neurochemistry were presented first, and the diseases were then considered seriatim as in textbooks of clinical neurology. To avoid this undesirable arrangement we have dealt with neurological disease in an order that has been determined chiefly by chemical considerations. We believe this approach allows the greater opportunity for the clinician to develop chemical insights. However, we have not simply taken chemical class as the primary criterion for determining the order in which neurological diseases are considered. Rather, we have seen in the complex patterns of chemical activities that occur in cells, groupings of reactions that serve particular functional purposes that appear especially germane to the interests of clinical neurology. We have built the book around an analysis of disorders of these functional biochemical reaction sequences (which, to a considerable extent, do correlate with chemical class).

1.2 THE FUNCTIONAL SIGNIFICANCE OF CERTAIN NEUROCHEMICAL REACTION SEQUENCES

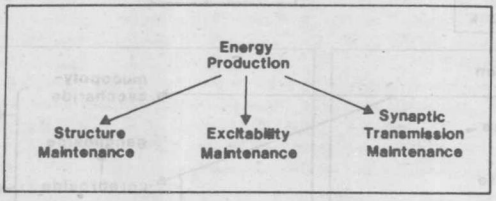
The nervous system is chiefly concerned with the rapid transmission of signals from point to point within the body. This transmission involves electrical conduction along preformed anatomical pathways which are kept in a state of excitability, and also chemical transmission across synaptic clefts between nerve cells and, at the periphery, between nerve cells and effector cells. One can conceive the main biochemical functions of neural tissue as involving the production of energy, required to drive chemical reactions serving various purposes, including:

(1) The synthesis and degradation of large molecules, required to maintain the structural integrity on which the function of neural tissue depends,

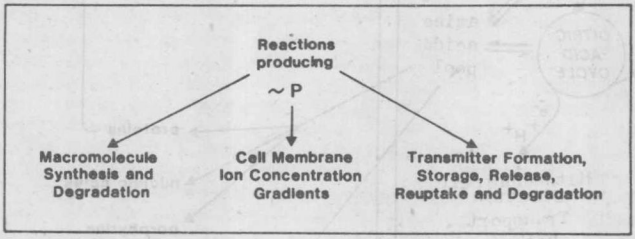
(2) The production of ionic concentration gradients, required to sustain nerve cell excitability, and

(3) The maintenance of the synaptic transmission process.

In addition, there are reactions of small metabolic intermediate molecules involved in various synthetic activities. The energy yielding reaction sequence and the reaction of small metabolic intermediate molecules are so intimately linked that they are conveniently considered together. Thus the functional concept



may be correlated with a concept of neurochemical processes.



Such a schematic overview embraces many important aspects of neural activity, though it does not bring out the mutual interdependence of the various processes. When one considers skeletal muscle function, certain different macromolecules become relevant, the whole matter of synaptic transmission is largely inapplicable, and high energy phosphate ($\sim$P) use is heavily directed towards muscle contraction rather than towards impulse conduction.

In this book, the disorders to be considered have been grouped according to which of the major neurochemical functions is primarily disturbed in each disorder. A disorder may, of course, produce consequent disturbance of biochemical mechanisms in a different functional category or categories, and the primary disturbance of molecular mechanisms (usually an enzyme defect) may not always be known with certainty. Consequently the classification of disorders here adopted may not prove valid in all instances, as knowledge grows.

It may now be useful to amplify to a limited extent the more important chemical reaction sequences involved in the major groups of neurological functions mentioned in Figure 1.1. These reaction sequences determine the subdivision of the contents of the various chapters of this book. In general, for each subdivision (i.e. a major group of related reactions) we have attempted to provide an initial account of the chemistry in sufficient detail for the clinician's purposes. We have then related known neurological disorders to this chemistry, attempting to emphasize principles and features common to a group of disorders, where possible. Then individual clinical disorders of each reaction sequence are dealt with briefly, but in a systematic fashion, under the

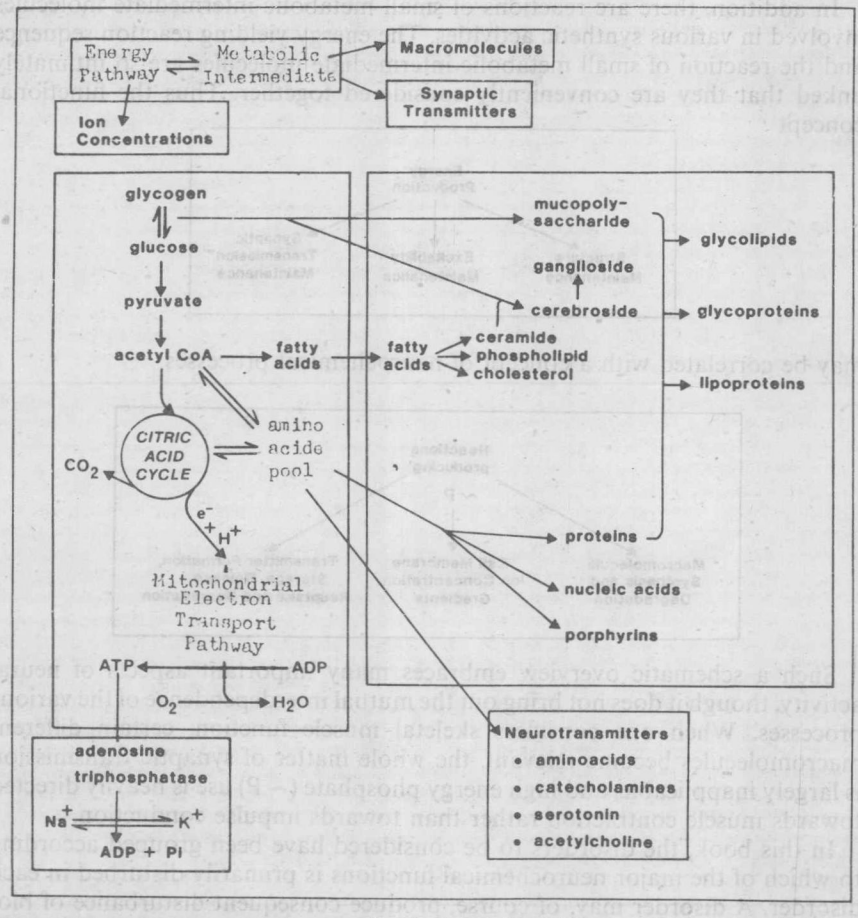


Figure 1.1 Major aspects of neurochemical activity, with the relevant chemical pathways (in outline)

following subheadings, unless the available material is too slight to warrant such subdivision:

(1) Introductory comment,
(2) Biochemical abnormality,
(3) Aetiology,
(4) Structural pathology,
(5) Clinical features,
(6) Diagnosis
  (a) clinical
  (b) laboratory,
(7) Treatment.

Such a structured approach may highlight gaps in knowledge which might be obscured by a less methodical presentation. Because of the interests of the intended major readership and the level at which the material is presented, details of biochemical analytical methods are not provided. However, the types of analytical method used in making biochemical diagnoses are indicated. By use of this information, and the references, those interested should be able to gain access to details of the relevant laboratory techniques. Many of the disorders considered here are rare, or comparatively rare. Therefore at times both clinicians and laboratory workers may find it preferable to use the references to make contact with those who have the appropriate chemical assays already functioning, rather than attempt to set up these assays for themselves to study one or two patients.