BIOCHEMISTRY
and the
CENTRAL NERVOUS SYSTEM

HENRY McILWAIN

SECOND EDITION

BIOCHEMISTRY AND THE CENTRAL NERVOUS SYSTEM

By

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PREFACE TO THE SECOND EDITION

THE present edition bears witness to the rapid development of biochemical studies of the central nervous system. About a quarter of the book is newly written, and a quarter of the work quoted has been published during the last three or four years. Where growth of the subject has been greatest, sections have been added; some three-quarters of the pages incorporate new knowledge. The object of the book remains unchanged, in giving a reasoned exposition of the current status of its subject to students and research workers in medicine and science, especially to those concerned with biochemistry, neurophysiology, neurochemistry, neurology and psychiatry.

In this rewriting, I have been greatly helped by discussions in this and other Institutes, including the National Institute of Neurological Diseases and Blindness of the United States Public Health Service. My especial thanks are due to Dr. P. J. Heald, R. Rodnight, Professor G. W. Harris, and my wife for their comments on the manuscript or proof; and to Messrs. J. & A. Churchill for the care which has been given in producing the book.

H. MCILWAIN.

PREFACE TO THE FIRST EDITION

THIS book has developed from research and from teaching in faculties both of medicine and science. Its subject forms part of teaching in physiology and in psychological medicine, in the University of London. In addition, the story of chemical change and structure in the central nervous system presents to the biochemist a well developed branch of his own subject and one which has often been in the forefront of biochemical discovery. Attention has been paid to each of these aspects in the present book.

Biochemistry and the central nervous system overlaps and adjoins several other subjects, notably pharmacology and endocrinology; each year some 3,000 papers appear which concern chemical substances or processes and the central nervous system. It has therefore been a major problem to decide how much to include in the present book. The solution chosen has been to include sufficient reference to neighbouring subjects to illustrate where they are applicable to biochemistry and the central nervous system, and it to the neighbouring subjects. When several aspects of the action of a drug can be seen to be linked by known biochemical mechanisms, these are indicated. When hormonal interactions with the central nervous system have as yet little biochemical logic, mention is brief or absent.

Because the subject of the present book extends beyond the limits of biochemistry itself, I have been most grateful for comments on it from Professor Aubrey Lewis and Professor Alfred Meyer, as well as from Professor F. Dickens and from members of the Department of Biochemistry of this Institute. It also owes much to informal discussion in this and in other departments where I have worked, including the Department of Physiology of the University of Chicago, and the Medical School at Dunedin, New Zealand. The last chapter contains material from the Christian Herter Lecture given at New York University College of Medicine in 1954.

H. MCILWAIN.

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CHAPTER 1

BIOCHEMICAL STUDIES OF THE BRAIN

When chemical investigation of the organs of the animal body developed about 1800, the gross anatomy of the central nervous system was familiar but little was known of its physiology and pathology. These, and especially the histology of the brain, grew to be major subjects during the nineteenth century. Biochemical and electrophysiological studies of the brain remained rudimentary until after the first quarter of the present century. Berger's discovery of rhythmic potential changes from the brain measurable outside the head was made in 1929; reasonably accurate measurement of respiration of cerebral systems began about 1920 with separated tissue, was obtained in perfused animals in 1939 but in normal human subjects not until 1947. Until recently, therefore, there has been much scope for speculation with respect to this most fundamental aspect of cerebral metabolism.

Electrophysiological and biochemical exploration of the brain are akin not only in the time of their commencement but also in the velocity of the processes with which they are concerned. Typical changes in electrical potential seen with the electroencephalogram occupy periods of 1 to 1/50 of a second. Changes observed by ordinary biochemical techniques usually take some minutes, but early in the exact study of cerebral constituents it was found necessary to measure processes lasting a second or less. Now one can estimate that during the 1/10 second occupied by a ripple of potential change at alpha frequency, appreciable proportions of many important cerebral metabolites are degraded or synthesized. Here one is dealing, not with the fastest cerebral processes in which voltage change and ion migration occupy only parts of a millisecond, but with processes occurring at speeds commensurate with ordinary impressions of the activities of the brain. Interrelations between biochemical and more overt aspects of cerebral functioning have played a large part in making this book. It remains, nevertheless, within a framework largely biochemical for in this manner can best be expressed the biochemical properties on which cerebral function is based and by which also it is characterized and restricted.

The Growth of Chemical Knowledge of the Brain

Metabolic studies of the brain though of recent development had notable precursors. During most of the past 150 years, investigation of the nervous system by chemical methods has attracted a reasonable

proportion of the chemical resources of the times. It has passed through many phases, which will now be briefly summarized in a fashion which introduces the literature of the subject.

Fractionation of Cerebral Constituents

The first satisfactory application of chemical methods to the brain was made in studying its composition. This commenced before chemistry had fully emerged as a science; Hensing's notable account dates from 1719. Other 18th-century writers contributed knowledge of inorganic constituents of the brain, but the realization that it and other organs contained a multiplicity of organic constituents did not come until about 1800. Vauquelin (1811) developed a type of investigation which almost became the standard chemical approach of the 19th century. By systematic use of an organic solvent and a heavy metal precipitant (ethanol and lead salts) he separated cerebral constituents to fractions with the intention of accounting for all the brain in terms of materials of definite composition. Of the many workers who developed this theme, Couerbe (1833) is noteworthy in attempting to show differences in the composition of the brain in mental disorder and Thudichum in the comprehensiveness of his study: *The Chemical Constitution of the Brain* (1884; 1901; see McIlwain, 1958*c*) lists some 140 constituents and carries a comprehensive bibliography. Because of the large proportion of fatty materials in the brain, much of this study concerned lipids. Although succinic acid and proteins also featured, it was their "chemical statics" with which, in Thudichum's own phrase, he was concerned. Fractionation of cerebral constituents from this point of view is still in progress; it represents an important route to chemical understanding and features prominently in the *Symposia* (1956*a*, *b*; 1957*b*) and *Colloquium* (1958).

Metabolic Studies

It is a mark of the distinctiveness of biochemistry as a discipline, that chemical fractionation of cerebral constituents gave a body of knowledge which did not in itself afford much understanding of cerebral functioning. To a much greater extent, this has come, as in physiology as a whole, by two main routes: by study of energy relationships and by the chemical characterization of substances which perform some specific role as substrate, intermediary metabolite, vitamin or enzyme. In the present account, as much quantitative information as possible has been collated about such substances and processes, specifically in the central nervous system. These aspects first received comprehensive treatment by Winterstein (1929) in his contributions on the *General Physiology of Nerve and of the Central Nervous System* to Bethe's *Hand-*

book. Peripheral nerve had then been studied in isolation, both biochemically and electrophysiologically, and such investigations were beginning also with the central nervous system. Winterstein's account of these investigations, to which his laboratory greatly contributed, is excellent in its description of relations between respiration, substrate utilization and functional activity. Possibly because his experimental work was largely with the frog, many of Winterstein's observations have been overlooked by subsequent writers. He could of necessity say little or nothing of intermediary metabolism.

This aspect is as far as possible supplied in Page's (1937) *Chemistry of the Brain* but, it is very significant, largely in terms of investigation with tissues from organs other than the brain. Several aspects of cerebral metabolism come to their own in Himwich's (1951) *Brain Metabolism and Cerebral Disorders*, especially those concerned with carbohydrate metabolism. They are also prominent in a Conference (1952) and in several Symposia (1952, 1955, 1956*a*, *b*; 1957*b*; 1959*a*, *b*) and Collected papers (1954, 1955).

Study of Substances acting on the Brain

Chemical factors were first recognized as capable of a major role in cerebral activities not by the metabolic studies just described, but rather by the spectacular way in which defined substances modified the activities of the brain. Lack of oxygen or the administration of alcohol or morphine were among the earliest examples, followed around 1850 by synthetic drugs developed specifically for their central effects, as has been recounted in *Chemotherapy and the Central Nervous System* (McIlwain, 1957). Chemical induction of changed mental states by such substances gave important data to those who, in the past century, invoked chemical factors in normal mental functioning and in its derangement in disease (McIlwain, 1955, 1958*a*, *b*). The subjects now often termed neuropharmacology and psychopharmacology have for some time formed a notable part of pharmacological texts, and have recently been the subject of separate *Symposia* (1956*c*, 1957*a*).

Neurochemistry

The various applications of chemistry to the study of the nervous system, which have been outlined in the preceding paragraphs, have in recent years increasingly received the collective designation of neurochemistry. The term *Nervenchemie* has since the 1850s meant, more literally, the chemistry of the nervous system (see Schlossberger, 1856). International Symposia in Neurochemistry commenced in 1954 and have to date concerned the development of the nervous system, its metabolism, and its chemical pathology. Collected papers entitled

Neurochemistry were published in 1955 and 1956, and the year 1956 saw the foundation of the *Journal of Neurochemistry*. A survey of neurochemistry (McIlwain, 1958*a*) indicated some 6 groups and 40 subgroups of chemical work within the specialty. A large part of this work has been published in journals of neurology and psychiatry, which in recent years have contained up to 40% of papers with pronounced chemical aspects. The bibliographies of the present book will be noted to contain many references to such journals, and year books in these subjects which also carry chemical aspects include *Recent Progress in Psychiatry*, *Progress in Neurology and Psychiatry* and the Research Publications of the *Association for Research in Nervous and Mental Disease*. Literature quoted in the present account is necessarily selected but is intended to cover or to lead to information on the greater part of the subject especially in its quantitative aspects.

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CHAPTER 2

METABOLISM OF THE BRAIN *IN SITU*

Substances exchanged between Blood and Brain

The brain is continually active, as is evident from ordinary experience and from the continuously fluctuating electrical potentials which can be detected in the head. No means are available for supporting such activity other than a continuous supply of substances to the brain by the bloodstream. The nature of these substances can be determined by analysing the blood which enters the brain from the heart. The substances taken from or added to the blood by the brain can be determined by comparing the composition of the blood entering the brain with the composition of that leaving it.

Many such determinations have now been carried out especially in man, so that information is available on cerebral metabolism in a variety of circumstances, and such information constitutes the larger part of this chapter. Blood from the heart can be sampled at any convenient artery, for example in man at the arm or the thigh; but there are relatively few points which afford a representative sample of venous blood from the brain. Among the most suitable in man is the internal jugular vein, especially at its superior bulb. When arterial and cerebral venous blood are analysed it is found that the greatest differences between them are in substances concerned in carbohydrate metabolism (Table 1). Blood constituents such as water, protein, total base or inorganic phosphate, show little change. The change in oxygen content is outstanding. It falls by about 6·7 ml./100 ml. of blood, which is a somewhat greater fall than is found to take place in oxygen when the blood traverses most of the other organs of the body. This is reflected in the relatively low value of 62% for the oxygen saturation level of the cerebral venous blood.

The briskness of normal cerebral respiration leads to enquiry as to the substrate oxidized. Its nature is indicated by the concomitant change in carbon dioxide which at 6·6 ml./100 ml. of blood is almost exactly equivalent to the oxygen absorbed; that is, the normal cerebral respiratory quotient is almost unity. This leads to the conclusion that, of blood constituents, glucose is most likely to be the main substance oxidized, and indeed the arteriovenous difference in glucose is found to be large. At 9·8 mg./100 ml. it is somewhat larger than is required to account for the oxygen used in respiration, so that even if all the

respiratory carbon dioxide is derived from glucose, other products requiring less oxygen for their formation must also be formed. One likely product is the lactic acid of Table 1, and a further product is pyruvic acid. These three substances, carbon dioxide, lactic acid and pyruvic acid, account remarkably completely for the glucose utilized by the human brain. In an instance (Himwich & Himwich, 1946) in which the arteriovenous difference in glucose was 10·2 mg./100 ml. of

Table 1

Chaages in blood on its passing through the brain

Constituent	Blood levels		Venous—Arterial levels (± standard deviation)	
	Arterial	Venous		
Oxygen:				
content (ml./100 ml.)	19·6	12·9	− 6·7	± 0·8
capacity (ml./100 ml.)	20·9	20·8	− 0·1	
saturation (%)	93·9	61·8	− 31·7	± 3·9
Carbon dioxide:				
content (ml./100 ml.)	48·2	54·8	+ 6·6	± 0·8
tension (mm. Hg)	39·9	49·9	+ 10·0	± 1·2
Glucose (mg./100 ml.)	92·0	82·0	− 9·8	± 1·7
Lactic acid (mg./100 ml.)	9·9	11·5	+ 1·6	± 0·9
pH at 38°C	7·42	7·37	− 0·05	
Inorganic phosphate (mg./100 ml.)	3·4	3·4	0	
Total base (mequiv./l. serum)	152·9	154·1	+ 1·2	± 1·2

The values are the mean results obtained by Gibbs, Lennox, Nims & Gibbs (1942) for 50 healthy men of 18–29 years of age, at rest. Blood was sampled at the internal jugular vein and femoral artery. The respiratory quotient was 0·99 ± 0·03.

blood, the carbon dioxide found was equivalent to 8·9 mg. of glucose/100 ml.; the lactic acid to 1·2 and the pyruvic acid to 0·2, a total 10·3 mg./100 ml. Also, by measurement of arteriovenous difference the human brain has been shown not to remove appreciable quantities of ketone bodies from the blood when these are present at unusually high level during starvation or diabetes (Mulder & Crandall, 1942).

Although under normal conditions glucose forms the main oxidizable substrate for other organs of the body as well as for the brain, the brain is unusual among the larger organs in its dependence on glucose. When

blood glucose falls, muscle, liver, or kidney oxidize other substrates and their level of functioning does not immediately change. The contrast in this respect between cerebral and muscular tissues is shown well in the experiment with dogs, fasted and rendered hypoglycaemic with insulin, which is quoted in Table 2. It is instructive to see that in the brain the fall in arteriovenous difference in oxygen paralleled that in glucose as blood glucose was lowered. Reduction of arterial glucose to 30 mg./100 ml. was associated with a small fall in each arteriovenous difference, while at 12 mg./100 ml. both had fallen considerably.

Table 2

Hypoglycaemia on oxidations in brain and muscle

Measurement	Arterial blood glucose (mg./100 ml.)	Arteriovenous difference	
		glucose (mg./100 ml.)	oxygen (ml.O_2/100 ml.)
Brain:			
Before experiment	90	13·1	9·3
Moderate hypoglycaemia	30	12·5	8·0
Intense hypoglycaemia	12	3·0	3·8
Muscle:			
Before experiment	90	7·6	6·9
Hypoglycaemia	20	1·7	6·0

Dogs were fasted and rendered hypoglycaemic with insulin (Himwich & Fazekas, 1937).

Changes in blood on its passing through skeletal muscle reacted differently to hypoglycaemia: at 20 mg. glucose/100 ml. arterial blood, the arteriovenous difference in glucose was less than one quarter of its normal value while oxygen uptake was little changed. Muscle therefore oxidizes substances other than glucose when glucose is lacking; the brain has only a limited ability to do so. This makes it understandable that it is cerebral function which fails in hypoglycaemia rather than, for example, muscular function: coma ensues with the heart still beating. These matters are examined more fully on pp. 13 to 15.

Measurement of Cerebral Metabolic Rates

The level of metabolic activity exhibited by an organ or by a tissue with respect to a particular substance is often best expressed as a metabolic rate. This gives the quantity of substance caused to react in unit time by unit weight of the organ or tissue. Measurements of

metabolic rate of the brain have usually been expressed in ml. or mg. of substance caused to react, per 100 g. fresh weight of brain per minute. Determination of change in concentration of a substance in the blood as it passes through the brain, gives one part of the data needed to express its activity as a metabolic rate. The other part of the data needed is the rate of flow of blood through the brain. Thus, when arterial blood loses 6·6 ml. of oxygen per 100 ml. on passing through the brain at the rate of 50 ml. per 100 g. of brain per minute, the cerebral respiratory rate is 6·6 × 50/100, or 3·3 ml. oxygen/100 g./min. This manner of expressing metabolic activity is valuable because, as will become evident later, the rate of blood flow through the brain varies greatly in different conditions and often in such a way that with decreased cerebral activity the flow slackens, while with increased activity it increases. Changed cerebral metabolism is thus only partly reflected in changed arterio-venous difference.

When comparing different cerebral metabolites, quantities of material are conveniently expressed in molar units. A cerebral respiratory rate of 3·3 ml. O_2/100 g. tissue/min. then becomes 3·3/22·4 = 0·147 mmoles/100 g./min. or 88·5 μmoles/g./hr. The utilization of glucose of 10·2 mg./100 ml. blood or 5·1 mg./100 g. tissue/min. corresponds to 5·1 × 60/180 or 1·7 mmoles/100 g./hr. This is 17 μmoles/g./hr., requiring 6 × 17 = 102 μmoles O_2/g./hr. for complete oxidation ($C_6H_{12}O_6 + 6O_2$). This is equivalent to the complete oxidation of about 85% of the glucose removed by the brain.

Methods

It is only relatively recently that adequate determinations of cerebral blood flow have been made in any animal under natural conditions of flow as distinct from those during perfusion. The determinations are of two main types. The first depends on dilution of a dyestuff and yields the volume of blood flowing through the brain as a whole, in unit time. The second depends on the diffusion of an inert substance to the brain from the blood, and gives the volume of blood flowing through a unit volume of cerebral tissue, in unit time. The two methods have given comparable results; in applying them the anatomy of the cerebral blood vessels in the particular species studied must be carefully considered.

A suggested procedure in applying dye-dilution methods is to inject Evans blue at a rapid constant speed to both carotid arteries and to collect venous blood from the internal jugular (Gibbs, Maxwell & Gibbs, 1947; Schmidt, 1950). The rate of blood flow then bears the same relationship to the rate of dye injection, as the concentration of dye in the solution injected does to the concentration of dye in the venous blood.

The method on which most of the results quoted below depend, is a diffusion method devised by Kety (1948) and Schmidt (1950; for a discussion of difficulties see the *Symposium*, 1937; Gregg & Shipley, 1944; Kety, 1955). The method has been applied largely to man and also to monkeys and to the dog. It depends on measuring the rate of entry to the brain of a foreign substance added to the blood. Nitrous oxide has been the most frequently-used foreign substance for it is freely diffusible, easily measured, and readily introduced to the bloodstream by inhalation. A radioactive form of the inert gas krypton has also been employed. Nitrous oxide is used as a mixture of about 15% N_2O, 20% O_2 and 65% N_2 which does not affect the subjects breathing it (80% N_2O with 20% O_2 can be excitant or depressant). From the lungs nitrous oxide passes to the heart and at uniform concentration to all parts of the body in arterial blood. During the first few minutes of inhalation, the blood flowing from an organ such as the brain contains less nitrous oxide than that entering it, because nitrous oxide is being lost to the substance of the brain. The more sluggish the flow of the blood, the greater is the arteriovenous difference in nitrous oxide, and the longer does it persist.

Four determinations of arterial and venous nitrous oxide in the first ten minutes after inhalation are sufficient to give both the rate of approach to equilibrium and its final value, which are required for calculating the rate of flow. The necessary samples are taken to syringes previously connected through taps to needles in the femoral artery and the superior bulb of the internal jugular vein. As, throughout, it is concentrations of N_2O which have been determined and not actual amounts, the rate of blood flow is obtained as a quantity per unit quantity of brain, and commonly expressed as ml. blood/100 g. brain/min.

Normal Values for Cerebral Respiratory Rate

The volume of blood flowing through the human brain is normally a considerable proportion of the total which the heart supplies to the body as a whole: about 15% in adults (Scheinberg & Stead, 1949; Folch, 1947), although the weight of their brain is only 2·5% of that of the body.

As noted above, blood flowing through the brain suffers a reduction in its oxygen content which is somewhat greater than that occurring in the blood in the rest of the body, and assessments of the ratio of oxygen absorbed cerebrally to that breathed show that 20–25% is removed by the brain. This is a surprisingly large proportion for an organ which performs no obvious external mechanical, osmotic or chemical work. It reflects the importance of the brain in higher animals and considera-

tion is given below to how the respiration of the brain supports its activities. It is of course under resting metabolic conditions that cerebral respiration accounts for such a large proportion of the oxygen breathed: that is, when the oxygen consumption of the body as a whole is

Table 3

Cerebral blood flow and respiratory rate in man

Condition (Adult subjects except as specified)	Cerebral blood flow (ml./100 g. tissue/min.)	Cerebral respiratory rate (ml. O_2/100 g. tissue/min.)
Children, mean age 6·2 years[9]	102	5·1
Normal resting subjects *A*[1]	54	3·3
Normal resting subjects *B*[2]	58	3·2
Normal subjects *C*, supine[6]	65	3·8
Normal subjects *C*, erect[6]	52	3·8
Hyperventilation[1]	34	3·7
Breathing 5–7% CO_2[1]	93	3·5
Breathing 85–100% O_2[1]	45	3·2
Breathing 10% O_2[1]	73	3·3
Insulin hypoglycaemia*[1] arterial glucose level 19 mg.%	61	2·6
Insulin coma*[1] arterial glucose level 9 mg.%	63	1·9
Irreversible insulin coma[8] arterial glucose, 360 mg.%	52	1·5
Natural sleep[10]	65	3·4
Thiopentone anaesthesia[1]	52	1·9
Thiopentone anaesthesia[3]	61	2·1
Thiopentone anaesthesia[4]	—	2·1
Schizophrenics[1]	54	3·3
Uremic subjects[2]	50	2·3
In diabetic acidosis[1]	45	2·7
In diabetic coma[1]	65	1·7
In myxedema[7]	40	2·8
Extreme apprehensiveness (occasionally; see text)[10]	—	5·0
Adrenaline perfusion (see text)[10]	61	4·2
In cerebral haemangioma[5]	164	3·3

* Carried out with schizophrenic subjects.

[1] Kety (1948). [2] Heyman *et al.* (1951). [3] Wechsler *et al.* (1951). [4] Himwich *et al.* (1947). [5] Schmidt (1950). [6] Scheinberg & Stead (1949); for comparison of these values with those for subjects *A*, see Kety (1955, 1957). [7] Scheinberg, Stead, Brannon & Warren (1950). [8] Fazekas, Alman & Parrish (1951). [9] Kennedy (1956). [10] Sokoloff (1956).