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Section 33 Volume I

Pharmacology of the Cerebral Circulation

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VOLUME I

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Section 33

PHARMACOLOGY OF THE CEREBRAL CIRCULATION

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VOLUME I

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ABBREVIATIONS USED IN THIS BOOK

A-V	:	arterio-venous difference
BBB	:	blood–brain barrier
CBF	:	cerebral blood flow
CMR	:	cerebral metabolic rate
CNS	:	central nervous system
CSF	:	cerebrospinal fluid
CV	:	cerebrovascular
CVR	:	cerebral vascular resistance
MABP	:	mean arterial blood pressure
ECF	:	extracellular fluid
ECS	:	extracellular space
EEG	:	electroencephalogram
PCO_2	:	partial pressure of CO_2
PO_2	:	partial pressure of O_2
rCBF	:	regional cerebral blood flow
rCMR	:	regional cerebral metabolic rate

PREFACE

IN THE course of the last 8 years numerous technological advances have led to impressive developments in brain-circulation studies. New functional aspects of brain circulation, new physiopathological processes and new therapeutical tendencies and trends have all been expounded. It is somewhat surprising, therefore, to note that brain-circulation pharmacology has fallen behind the other branches of cerebrovascular investigation, thereby indicating that pharmacologists would appear to be rather unconcerned about brain-circulation problems.

This book wishes to demonstrate that this attitude is not justified, and that pharmacological studies performed on experimental animals (which represent the starting point of any well-grounded pharmaco-therapeutical study) have a right to full citizenship in the field of cerebral circulation too. Thus, in recent times, new pharmaco-therapeutical trends have been suggested as the result of clinical observations of the "steal" and "counter-steal" phenomena; in fact, it is not by mere chance alone that these phenomena reflect a principle set forth some time ago by experimental pharmacologists, namely the interrelationships between cerebrovascular reactivity and the functional status of brain circulation.

The reason why experimental pharmacology was not able to, or did not, keep up with the rate of progress achieved by studies on other aspects of brain circulation may be explained in many ways. The part played by technical considerations has been dealt with in this book, but other non-technical factors (for example, the high cost of the experimental research in this field and the limited possibility of rapidly obtaining highly profitable results) have also played their indisputable roles. Therefore, even in the brain-circulation field, we have been faced with the very general and crucial problem of the heavy, and sometimes critical, influence exerted by non-technical motivations in the progress of basic research.

Some aspects of this book will appear rather unusual for a text dealing with pharmacology. Only a certain number of chapters are devoted strictly to the mode and mechanism of the cerebrovascular action of different drugs. A significant part of the book does, however, deal with the physiological, physiopathological and clinico-therapeutical aspects of brain circulation. This part intends to point out some of the gaps still existing in the field of brain-circula-

tion pharmacology. Thus, the chapter dealing with blood–brain exchanges introduces a subject which should be more carefully considered in order to remove future work on brain circulation from the sphere of pure theoretical considerations. The chapters on the physiopathological and clinico-therapeutical aspects of brain circulation are intended to inform the pharmacologist on the possible mechanisms by which well-known drugs, and new drugs, exert, or may exert, their therapeutical effects on brain disturbances of vascular origin.

It has been said, and written, that a book may be useful also as a result of the gaps contained and the unwritten chapters. This is certainly true if the existence and origin of these gaps are discussed and a possible way to write the missing chapters is indicated. This has been the principal aim of this book, which comes about as the result of frank, but also critical, co-operation between the authors. Any success that this book may achieve, therefore, will reflect credit equally on the authors and editor.

AMILCARE CARPI

CONTENTS

CHAPTER 1

THE PHYSIOLOGY OF CEREBRAL CIRCULATION

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NORMAL VALUES AND METHODOLOGY

The cerebral blood flow in healthy adult subjects is about 50 ml. of blood per 100 g tissue per minute. This value, related to the average brain weight, corresponds to a flow of about 750 ml./min for the whole brain. Thus, although the brain weight is only 2–3 per cent of the total body mass, it takes about 20 per cent of the resting cardiac output. Such high perfusion is related to an equally high metabolic rate. In fact, the oxygen metabolic requirement of the brain is about 3 ml./100 g/min, or 45 ml./min for the entire organ, which is 25 per cent of the total O_2 consumption of man at rest.

The metabolic rate and hence the flow are not uniform throughout the brain, although similar in the two hemispheres (Shinohara *et al.*, 1969). CMR for O_2 and CBF are higher in the densely cellular gray matter than in the white matter as shown by the autoradiographic technique with ^{14}C antipyrine which measures blood flow in discrete areas of the brain (Landau *et al.*, 1955; Reivich *et al.*, 1969). Autoradiography has shown that the brain is composed of a large number of structures with different blood-flow rates (Table 1). Measurements of blood flow in the cerebral cortex, the caudate nucleus and the subcortical

TABLE 1. LOCAL CBF IN THE CONSCIOUS CAT

Structure	Local CBF (ml/g/min) mean ± s.e.
Sensory-motor cortex	1·38 ± 0·12
Caudate nucleus	1·10 ± 0·08
Thalamus	1·03 ± 0·05
Cerebellum	0·79 ± 0·05
White matter	0·23 ± 0·02

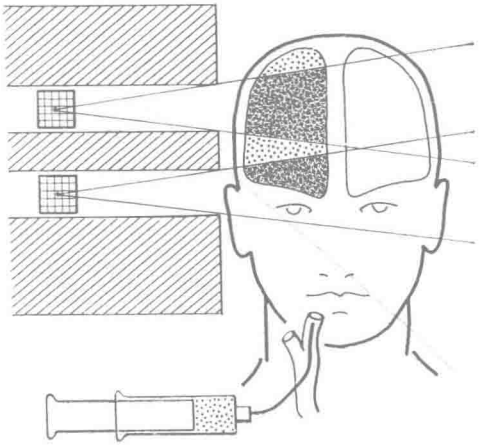
From Landau *et al.* (1955), by courtesy of the American Neurological Association.

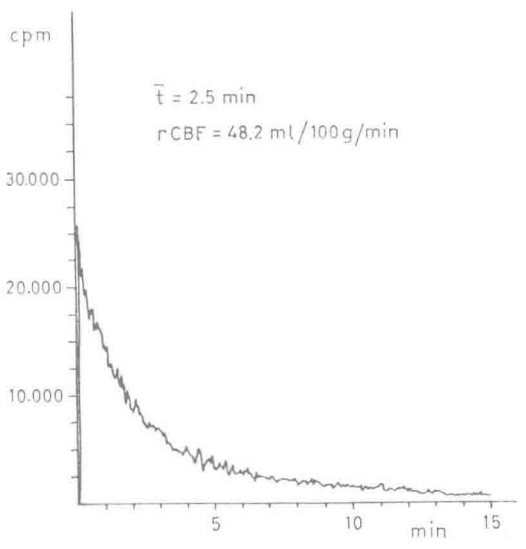
white matter by clearance methods (Ingvar and Lassen, 1962; Fieschi *et al.*, 1964, 1965) have confirmed the autoradiographic data.

In spite of the different values of blood flow in different regions of the brain there is a clear-cut bimodal distribution of blood-flow rates in the brain (Fig. 1); in this distribution, the modes correspond to the average blood flow to the gray and white structures of the brain. The existence of two distinct patterns of flow in brain, high values for the gray matter and low values for the white matter, has been used for calculation of the blood flow in different regions of the human brain from the extracranially registered clearance curves of a radioactive inert gas (regional cerebral blood flow). This technique, first described by Lassen *et al.* (1963), is the method of choice for physiological as well as for pharmacological and clinical studies in man.

Radioactive isotopes of inert gases, e.g. ^{133}Xe, ^{135}Xe, ^{85}Kr, ^{85m}Kr, are used as tracers. The basic assumption of these techniques is that there are no barriers limiting the diffusion of the gas between the tissue and the blood. This implies that the equilibrium of gas between the tissue and the blood perfusing it is continuous and instantaneous (Kety, 1951). In this situation, the "mean transit time" of the tracer in the region explored and the "clearance" or "washout rate", in the case of homogeneously perfused tissues, depend only on the blood flow and on the solubility ratio of the gas in tissue and blood; this value is known as the partition coefficient λ. Since the partition coefficient is a constant, the mean transit time and the clearance rate are linear functions of the blood flow through that tissue (Fieschi, 1965; Lassen and Høedt-Rasmussen, 1967).

Changes in concentration of the gamma-emitting radioactive tracer in the brain tissue of man can be recorded from the surface of the head (Fig. 2). Two to three ml. of saline equilibrated with the radioactive gas (approximately 1 mc/ml.) are injected in less than 3 sec into the internal carotid artery, this ensuring that the isotope is distributed to the brain only. For the 10 to 15 min following the injection, curves of radioactivity are recorded by several external detectors. The clearance curve of a diffusible indicator, in the absence of recirculation, can be analysed into two exponential components, showing the average blood-flow values and, in addition, an estimate of the mean flow of the fast and of the slow components and their relative weights (Fig. 2). These four values indicate the flow and the weight of the gray and white matter of the brain. Høedt-Rasmussen *et al.* (1967) and Hutten and Brock (1969) have suggested a non-compartmental analytical approach, based on a stochastic model, to obtain the average rCBF from the mean transit time of the diffusible indicator. Such analyses, however, are completely reliable only if radioactivity is measured with equal efficiency from all parts of the region explored. Measurements *in vivo* deviate from the ideal situation for a number of reasons. These





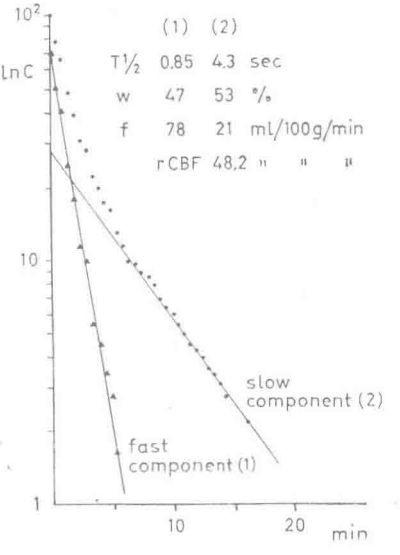


FIG. 2. *Top:* registration of the clearance curve of ^{85}Kr injected into the internal carotid artery. *Bottom left:* actual record of the clearance curve. Regional blood flow can be calculated from the mean transit time ($\bar{t}$ = area/height of the curve) on the basis of the equation:

$$\frac{1}{\bar{t}} = \frac{F}{V_{Kr^{85}}} = \frac{F}{\bar{\lambda}\ W} \times 100$$

where F = rCBF (ml/100 g/min); $V_{Kr^{85}}$ = volume of distribution of ^{85}Kr; $\bar{\lambda}$ = mean partition coefficient of ^{85}Kr (1·09); W = unit weight of the brain (1 g). *Bottom right:* semilogarithmic plot of the clearance curve. Two exponential

Continued overleaf

limiting factors vary according to experimental conditions, such as the collimation and detection systems and the isotope used. For example, resolution and efficiency are poorer with the weak energy of ^{133}Xe than with the stronger energy of the gamma emission of ^{85}Kr, and are even better with ^{135}Xe.

When these methods are used in clinical studies on individual patients, it is important to know the size of the experimental error. Data obtained with ^{85}Kr as a tracer, using five large detectors with crystals of 1·5 in. recessed 3 cm, pulse height analyser and digital ratemeters (Fieschi *et al.*, 1968) showed that, in normal subjects in the resting state, the mean rCBF was 45 ml./100 g/min, and the standard deviation of two subsequent measurements from the same region was 7·5 per cent. Therefore, only differences between two consecutive measurements exceeding twice the limits of this deviation (6·9 ml./100 g/min) are significant; for inter-regional measurements, only differences greater than 34 per cent are significant. In other laboratories the errors may be different depending on the experimental conditions; they are bound to increase when using sixteen or thirty-five probes of smaller size (Fig. 3).

Certain technological advances have been recently suggested: (i) using a shorter recording time, and limiting evaluation of the curve to the initial 2 min (the initial slope method; Hutten and Brock, 1969) and, (ii) an entirely automatic system of data processing using a direct spatial presentation of the regional blood-flow values (Fig. 3) (Sveinsdottir *et al.*, 1969; Fig. 3).

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components are evident, showing the blood flow rates of the fast (f_1) and the slow (f_2) compartments and their relative weights (w_1 and w_2). Compartmental analysis is based on the following equations:

$$C(t) = I_1 e^{-k_1 t} + I_2 e^{-k_2 t}$$

where C = recorded radioactivity; I_1 and I_2 = intercepts with the y-axis of the fast and the slow components; k_1 and k_2 = slopes of the fast and the slow components.

$$\text{rCBF} = \frac{I_1\lambda_1 k_1 + I^*_2\lambda_2 k_2}{I_1 + I^*_2} \times 100 \quad \text{(ml/100 g/min)}$$

where λ_1 (= 0·95) and λ_2 (= 1·30) = partition coefficients of ^{85}Kr for the fast and the slow components; I^*_2 = intercept of the slow component corrected for the short injection time and partition coefficient

$$\left(I^*_2 = I_2 \frac{\lambda_1 k_1}{\lambda_2 k_2} \right)$$

$$w_1 = \frac{I_1}{I_1 + I^*_2} \times 100 \quad ; \quad w_2 = \frac{I_2}{I_1 + I^*_2} \times 100 \quad (\%)$$

$$f_1 = k_1\lambda_1 \times 100 \quad ; \quad f_2 = k_2\lambda_2 \times 100 \quad \text{(ml/100 g/min)}$$

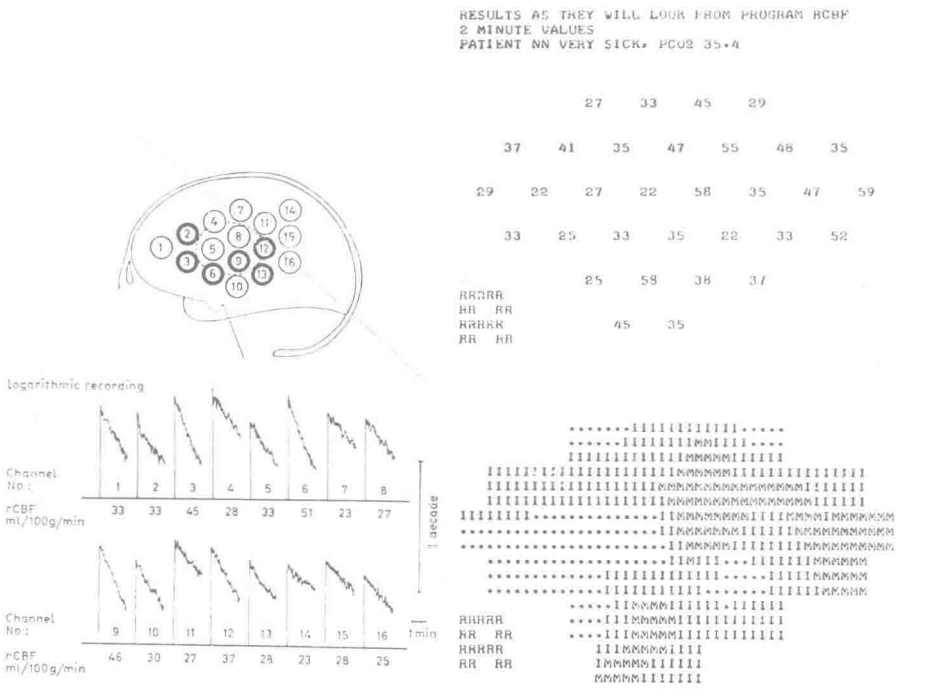

FIG. 3. *Left:* rCBF measured with ^{133}Xe in sixteen regions. The evaluation of the curves is limited to the initial two minutes. *Right:* further reduction of the size of probes allows rCBF to be measured in up to thirty-five regions. Use of a small digital computer on line gives the rCBF values in real time (numbers in the upper part of the figures = rCBF in ml/100 g/min) along with a graphical representation of the regions with increased (MM) and decreased (. .) blood flow. The symbol R indicates that the right side has been explored. Courtesy of Dr. N. A. Lassen.

CEREBRAL BLOOD FLOW UNDER DIFFERENT PHYSIOLOGICAL CONDITIONS

AGE

Recent studies in fetal lambs showed that CBF and CMR for O_2 and glucose increase gradually relative to brain weight; consequently, when CBF and CMR are expressed in ml./100 g/min, there are no changes in blood perfusion and oxygen and glucose consumption in the fetal brain during the second half of gestation (Mann, 1970; Rudolph and Heymann, 1970).

Kety (1956) has plotted the cerebral blood flow and CMR for O_2 measured by different authors in normal subjects from 5 to 93 years of age (Fig. 4). According to Kety's data the cerebral blood flow and the CMR for O_2 are very high during the first 10 years of life, and decrease somewhat abruptly in adolescence (see p. 205). Thereafter the blood flow and the CMR for O_2 both

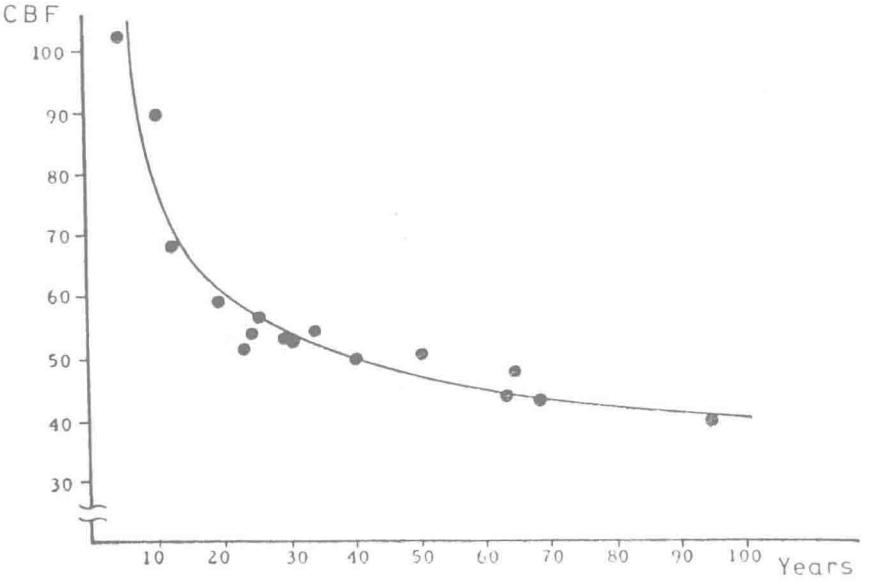

FIG. 4. Changes of CBF with aging in normal subjects. From Kety (1956).

decrease progressively. These data are in agreement with the progressive reduction with age of the O_2 tension of the cerebrospinal fluid of the cisterna magna, which is equilibrated with the O_2 capillary tension of the brain (Jarnum *et al.*, 1964).

Subsequent studies have shown that the CBF and CMR for O_2 were the same in young adults and healthy elderly subjects of average age 71. All these subjects were entirely free from physical and mental disease and scored above average for age tests of cognitive function (Dastur *et al.*, 1963). Such data cast some doubt upon the assumption that the decrease of blood flow and metabolism during old age is a truly physiological phenomenon.