Diurnal variations of whole blood serotonin content in patients with depression and neurosis

Clinical studies have provided evidence that serotonin (5-hydroxytryptamine, 5HT) is implicated in the state of depression, as its precursors, selective inhibitors of uptake and 5HT₂ receptor blockers are very effective in its treatment.^{1,2} There is some evidence that disturbances in the regulation of circadian rhythms may be of prime importance in the pathophysiology of affective disorders.³ Furthermore, depression is believed to be linked with brain serotonin metabolism.^{4,5}

As human blood platelets may be regarded as a reliable model for serotonergic synapse because of their specific biochemical mechanisms for uptake, storage, metabolism and release of amine, the whole blood measurement of serotonin (that is, mainly platelet serotonin, since very little is detectable outside the platelets) provides a peripheral model for the study of processes in the brain.^{6,7} However, it is still an open question as to whether blood platelet parameters reflect those in the brain. The daily fluctuations of behaviour in affective disorders have stimulated us to search for circadianism of serotonin.

We examined at five time points whole blood 5HT levels in psychiatric patients in hospital and control volunteers. The group of patients consisted of 18 subjects (12 with depression and six with neurosis). They were diagnosed and treated in the Department of Psychiatry, Hamamatsu University School of Medicine. At the time the blood samples were taken, patients were in a depressive state, confirmed by a mean score of 18.7 (range 12–24) on the 24-item scale of Hamilton Depression Rating Scale.⁸ None of them were receiving any drug, except for small doses of benzodiazepines, for at least 10 days before blood was taken. Before entering the trial, the patients were in good physical health and gave voluntary consent to participate. Ethical committee approval for this study was obtained from the Hamamatsu University School of Medicine. The control group matched for age and sex with the patients was made up of 30 volunteers, who showed no clinical signs of depression or organic disease, and were drug-free.

Quantitative analysis of 5HT in the blood was performed by HPLC as described by Anderson *et al.*⁹ Analytical recoveries were 85% (SD 4.5%, CV 5.6%). Amount and response for standards were linearly related.

As shown in the figure, whole blood serotonin level was significantly reduced in

depressed patients at 8:30, 10:30, 12:30, and 14:30 ($p < 0.01$), as well as in patients with neurosis at 8:30, 10:30, and 12:30. The values at 16:30 were similar in all groups. The blood concentration of 5HT showed a circadian change. In the depressed patients group the lowest value was obtained at 8:30 and the level progressively increased to 16:30. The values at 10:30, 12:30, 14:30 and 16:30 were significantly higher than that at 8:30 ($p < 0.05$). Fluctuation in whole blood serotonin level was observed in a group of patients with neurosis. The highest values were obtained at 8:30 and 14:30. From 8:30 it decreased gradually to 12:30 and showed a significantly lower value at 10:30 and 12:30 ($p < 0.05$). From 12:30 serotonin level in neurotic patients increased to 14:30 and remained at almost the same level at 16:30. The different pattern was shown in the control group. The highest value was obtained at 8:30 and it decreased gradually at 12:30, 14:30, and 16:30 ($p < 0.01$).

Since the characteristics of MAO activity, 5HT uptake, imipramine and alpha 2-adrenergic receptor binding are similar in platelet and brain, the platelet is one of the most researched biological markers in psychiatry. Platelet serotonin content is most likely regulated by the 5HT transport activity. Daily variations in serotonin uptake in depressed patients have been reported by several groups.^{10–12} A diurnal variation in the transport capacity is suggested by data reported by Modai *et al.*¹² The findings in our study support these observations. The second diagnostic feature of blood platelet is imipramine binding. Recent findings of reduced ³H-imipramine binding in platelet of depressed patients compared with healthy controls have been proposed as a biological marker of depression. However, there was no evidence for significant diurnal or circannual variation in the binding parameters in any of the diagnostic category.¹³

In conclusion, our data indicate that the clear distinct pattern of diurnal rhythm could be established in a group of patients with depression, neurosis as well as in a control group. Moreover, we found general differences in the circadianism of 5HT between depressed and neurotic patients, which may have practical implication in the differential diagnosis.

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- 1 Cowen PJ. Recent views on the role of 5-hydroxytryptamine in depression. *Curr Opin Psychiatry* 1988;3:56–9.
- 2 Coppen AJ, Doogan DP. Serotonin and its place in the pathogenesis of depression. *J Clin Psychiatry* 1988;49 (suppl):4–11.
- 3 Wehr TA, Goodwin FK. Biological rhythms and psychiatry. In: Arieti S, Brodie HKH, eds. *American handbook of psychiatry*. New York: Basic, 1981:46–74.
- 4 Grahame-Smith DG. Serotonin function in affective disorders. *Acta Psychiatr Scand* 1989;80 (suppl):7–12.
- 5 Curzon G. Transmitter amines in depression. *Psychol Med* 1982;12:465–70.

- 6 Coppen AJ, Turner P, Rowsell AR. 5-hydroxytryptamine (serotonin) in the whole-blood of patients with depression. *Postgrad Med* 1976;52:156–8.
- 7 Pletscher A. Platelets as models: use and limitations. *Experientia* 1988;44:152–5.
- 8 Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1967;6:278–96.
- 9 Anderson GM, Young JG, Cohen DJ, Schlicht KR, Patel N. Liquid-chromatographic determination of serotonin and tryptophan in whole blood and plasma. *Clin Chem* 1981;5:775–6.
- 10 Humphries LL, Shirley P, Allen M, Codd EE, Walker RF. Daily patterns of serotonin uptake in platelets from psychiatric patients and control volunteers. *Biol Psychiatry* 1985;20:1073–81.
- 11 Rausch JK, Shah NS, Burch EA, Donald AG. Platelet serotonin uptake in depressed patients: circadian effect. *Biol Psychiatry* 1982;17:121–8.
- 12 Modai I, Malmgren R, Asberg M, Beving H. Circadian rhythm of serotonin transport in human platelets. *Psychopharmacology* 1986;88:493–5.
- 13 Baron M, Barkai A, Kowalik S, Fieve RR, Quitkin F, Gruen R. Diurnal and circannual variation in platelet ³H-imipramine binding: comparative data on normal and affectively ill subjects. *Neuropsychobiology* 1988;19:9–11.

BOOK REVIEWS

All titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the United Kingdom and for members of the British Forces Overseas, but overseas customers should add £2 per item for postage and packing. Payment can be made by cheque in sterling drawn on a United Kingdom bank, or by credit card (Mastercard, Visa or American Express) stating card number, expiry date, and your full name.

Benjamin's Son: Benjamin Archer Kent MD. (1808–1864). By PETER H SCHURR. (Pp 193; £12.95 H/Back; £7.95 S/Back.) 1991. London, Royal Society of Medicine Services Ltd. ISBN 1-85315-146-7/1-85315-145-9.

This is a painstaking and devoted account of the life of an unusual physician of the 19th Century and his family connections. It is a fascinating document of social and medical history, and will therefore have specific appeal to those who have aptitude and inclination in this field. This book may not be read widely, which is a pity and I commend it to a wider public despite a certain ponderous idealism which clings to the early 19th Century and knowing of the general lack of sympathy for simple scientific methodology that prevails in our enlightened age.

The MD Thesis contained in translation in the Appendix with associated reviews of contemporary knowledge of the sympathetic ganglia by Peter Schurr, and the historical review of nervous disorders by Edward Hare, have the sympathetic ganglia as their

Figure Diurnal variations in whole blood serotonin concentrations. Each point represents the mean $\pm$ SE value (Duncan's multiple range test).

subject matter. Benjamin Kent delineates hypochondriasis, hysteria and dyspepsia and deduces the innate seat of hypochondriasis as the semilunar ganglion and the solar plexus. He discusses the structure and function of the sympathetic ganglia: those "small, unformed parts of the nervous system", the "tiny brains" of Winslow. Edward Hare points out that we are still to find the organic locus for these complex psychological syndromes and we still lack the chalybeate of Sydenham whereby the drooping spirits are roused and revived. The genuine interest of the MD Thesis lies in the chronic inability to solve the mind-body problem by scientific method or by Cartesian dualism. The book creates a broad sympathy for early 19th century life, and for the personal fortitude of Benjamin Kent. It is a sensitive portrait of an extended family and its friendships.

Benjamin Kent graduated LLMSA and MD from the University of Edinburgh, was granted the MRCP without examination in the very year that the diploma was instituted as a College examination. He practised as a general practitioner and as a physician in Harley Street; he became a brickmaker, a flour miller, and lived in fear of bankruptcy. He also was a founder physician of the Adelaide Hospital, and gave the first ether anaesthetic in Southern Australia, to a patient who underwent mastectomy for carcinoma. He was grand master of the Freemasons order, and died unexpectedly after a successful cataract operation.

I enjoyed this book and commend it. It is written with charm and an eye for detail, and with the skill, interest and the precise thoroughness which one would expect from careful neurosurgery.

JR HERON

Handbook of Neurology. By CHARLES WARLOW. (Pp 590; Price £29.50.) Oxford, Blackwell Scientific Publications, 1991. ISBN 0-632-01113-0.

Time was, when the more cerebral neurologists on the London scene, after a search of the literature, current neurological texts and their own experience would prepare their personal textbook of neurology. Most books were composed by the individual, without co-author or manuscript reader, each were given what was deemed to be a title suitable for the aims of the work. Thus we had Textbooks of Neurology, Essentials, Aids and many "Diseases of the Nervous System", with one long-term runner.

It has become the fashion for almost all neurologists practising in the "academic environment" to consider a title, a new format and express his understanding of and approach to the diagnosis and management of patients with neurological disease.

We now have another handbook of neurology which makes no claim to rival its ancestral 40 volume equivalent, but asserts a usefulness to specialists in other fields, neurologists in training, primary health care physicians and perhaps medical students. This is a book which does not attempt to address the problems of neurochemistry, neurophysiology, molecular biology nor immunology but considers simple neuroanatomy and disorders of importance and high incidence in the United Kingdom.

The author's approach is different from that in the traditional textbook. He divides his material by symptom headings and a general classification of neurological disease and peppers the text with lists, saving considerable space and sparing literary effort. We are given, for example a list of 52 drugs known to cause seizures. If you prefer lists to prose then this book should attract you.

Written in New Zealand during sabbatical leave and with a script scrutinised by 25 of Professor Warlow's peers, the book presents a refreshingly unconventional approach to the material. It is accurate in actuality and at times, capriciously provocative.

It has been said elsewhere that the major scientific advance in recent neurological practice has been the computer. The author considers the telephone to be the most important instrument at our disposal, but does not include it in his index!

As a short book of reference I feel that this true "handbook" will be very successful, but who is next and what will be new?

JB FOSTER

Hugh Cairns, First Nuffield Professor of Surgery, University of Oxford. By GJ FRAENKEL (Pp 296; Price £35.00). Oxford University Press, 1991. ISBN 019 262095 9

Sir Hugh Cairns, one of the three pioneers of specialised neurosurgery in Britain, died in 1952, at the age of 56. His influence spread far beyond these shores and it is appropriate that his biography should have been written by Professor Fraenkel, whose first encounter with Cairns was as a student in Oxford and whose career encompassed New Zealand and Australia.

Cairns was born in South Australia. His first venture abroad was as an orderly in the AAMC on the island of Lemnos during the Gallipoli campaign. He then returned home, completed medical qualification and was awarded a Rhodes scholarship. Before taking this up he served as a medical officer on the Western front. His initial stay in Oxford was eventful: work with Sherrington, a rowing blue and engagement to be married. He was increasingly drawn towards surgery and held junior posts in Oxford and at the London Hospital, eventually being appointed to the honorary staff. The turning point in his career was the award of a Rockefeller Scholarship to work under Harvey Cushing.

It is evident from his letters home that Cairns greatly admired Cushing's surgery but much disliked the man. Anyone who worked with Cairns will recognise the irony of his complaint of being overworked in Boston. The account of the subsequent struggle to establish himself as a neurosurgeon in the now almost unrecognisable world of the voluntary hospitals of London makes fascinating reading. Needless to say, he was successful for, as Professor Gardner wrote: "he was constitutionally unable to give up any project on which he had set his mind and heart".

Cairns' vital role in the establishment of the Oxford clinical medical school, although originally intended for post-graduates, is well known and is here fully described. This was immediately followed by the outbreak of war. Cairns' influence on the treatment and

prevention of head wounds was extensive and included St Hugh's head injury hospital, the organisation of mobile neurosurgical units in the field, and insistence on an effective helmet for dispatch riders.

The biographer must steer a narrow course between too much and too little detail and perhaps Fraenkel has erred a little in the former direction. In the profusion of names and dates it is difficult to recapture the atmosphere of the Nuffield of early days: the devoted but often exhausted house surgeons striving far into the night to write notes of the meticulous standard demanded in a room dominated by a gigantic Bjerrum's screen: the Monday ward round with Cairns full of vigour to the end while all else wilted: the stern reproof for not testing the sense of smell in a patient with a spinal tumour. "Better get it done, boy".

Hugh Cairns was a man of immense determination and energy whose personality attracted others to work enthusiastically with him in surgery, neurology, pathology, radiology and anaesthetics, but none worked as hard as he did himself. Was he a good surgeon? He, apparently, did not think so. He was certainly remarkably slow and not notably equable in the theatre. I still have vivid memories of having the privilege of assisting him while a medical student and being sharply reminded that this was brain and not plasticine that we were handling.

When he knew he was dying Cairns' reaction was one of anger that his plans for future work would not be completed. His achievements, amply documented by Gus Fraenkel, were already sufficient to satisfy most mortals.

WB MATTHEWS

Principles of Neurosurgery. Edited by R G GROSSMAN AND W J HAMILTON. (Pp 484; Price \$199.00). New York, Raven Press, 1991. ISBN 0 88167 750 7

One of the accepted definitions of the word "principle" is that it is a fundamental basis from which other actions or conclusions may be derived. This book is therefore somewhat mis-named since it is indeed a review of a very wide series of neurosurgical conditions, some of which are dealt with in considerable detail while others are only briefly addressed. In any multi-author text book the standard of the contributions is somewhat variable and often reflects the particular interests of the individual concerned.

Thus, in the first chapter on Anaesthesia Dr Albin's concern with Brain Retractor Pressure leads to a summary of some excellent work which he and his group have performed, and is of great interest. On the other hand it is somewhat doubtful whether the chapters on Congenital and Developmental Cranial Abnormalities and Primary Diseases of the Skull, both of which are extremely brief, should be included in a book claiming to address itself to fundamental principles of neurosurgery. The chapter on Spontaneous Intracerebral Haematomas fails to mention cavernoma, and the description therefore of Brainstem Haematoma is incomplete and by present standards inaccurate. In the same way, the coverage of Aneurysms, Arteriovenous Malformations and Brain Tumours is quite remarkably patchy. Thus Olfactory