Age and Ageing 1985;**14**:71–75

D. A. PHIPPS
Senior Lecturer
Liverpool Polytechnic,
Liverpool

C. POWELL*
Senior Lecturer
Subdepartment of
Geriatric Medicine,
University of Liverpool

PLASMA TRYPTOPHAN, AGE AND DEPRESSION

Summary

Plasma, obtained from 131 nondepressed, otherwise healthy subjects aged from 17 to 102 years, and 22 depressed subjects aged over 70 years, was analysed for total and free tryptophan. Variation with age was found in total tryptophan. This association has not been described hitherto. There was a significant increase in total tryptophan and a non-significant increase in free tryptophan with depression. This is in contrast to some studies in younger people showing a decline in plasma tryptophan in depressed subjects.

Introduction

Depression is a common illness in elderly people, being reported in some 10% of the over sixty-fives living at home (1). There is little published work specifically on changes in brain biochemistry in the elderly whether depressed or not.

It has been suggested that the biochemical basis of depressive illness may well be a relative or functional deficiency of serotonin and perhaps its precursor tryptophan (2, 3). We studied plasma tryptophan as an index of brain tryptophan.

Tryptophan in plasma may be divided into three fractions: (a) tryptophan incorporated irreversibly into the structure of the serum proteins, (b) non-protein tryptophan bound reversibly to plasma albumin, and (c) free tryptophan which is in equilibrium with the albumin-bound fraction. Free tryptophan is selectively transported across the blood–brain barrier by a competitive system which also transports other large neutral amino acids (4). The relative importance of the three factors, viz. total tryptophan (albumin-bound and free), free tryptophan and the ratio of tryptophan to competing amino acids, is disputed. From animal studies, some regard the free tryptophan as the most important (5–7). Others emphasize the ratio of tryptophan to competing amino acids (8–10). It has been suggested (9, 11) that the blood–brain barrier carrier system has the ability to strip competitively tryptophan from the albumin-bound fraction. On this view, the component of plasma tryptophan essential for provision of brain tryptophan includes both the free and a proportion of the albumin-bound fraction.

Results in humans are also conflicting. Low free tryptophan associated with depression (3), normal levels (12) and raised levels (13) have been reported.

*Address requests for reprints to Dr C. Powell, Department of Geriatric Medicine, St Boniface Hospital, 409 Tache Avenue, Winnipeg, Manitoba, Canada, R2H 2A6.

Often earlier studies failed to differentiate clinical subgroups of depression or did not control for drugs and diet. Drugs may displace tryptophan from albumin binding (14) (Table I). Variations in plasma non-esterified fatty acids (NEFA) also affect plasma tryptophan (15). These dietary influences can be disregarded if fasting blood specimens are obtained and unusual dietary habits are excluded.

We sought to determine: (a) whether plasma tryptophan varies with age using a wider age range of subjects than reported hitherto; and (b) whether depressed elderly people exhibit changes in free and total tryptophan as some had reported in younger depressives.

Table I. Drugs and plasma tryptophan

Drugs displacing albumin-bound fraction	*Drugs changing non-esterified fatty acids*
Salicylates	Noradrenaline
Indomethacin	Aminophylline
Phenylbutazone	L-Dopa
Clofibrate	Nicotinic acid
Probenecid	Insulin
Thiopentone	
Chlordiazepoxide	

Methods

Biochemical methods

Total and free plasma tryptophan, plasma cortisol, albumin and free fatty acids were analysed using standard methods (details available from the authors). Samples were analysed within 24 hours of collection by a biochemist who was unaware of the subjects' ages and mental status.

Subjects

Non-depressed healthy volunteers were recruited, comprising undergraduates, qualified rehabilitation therapists, nurses and university faculty members, and well elderly people who were relatives and friends of patients of the South-Central Liverpool Geriatric Service.

The depressed subjects studied were patients aged 70 years and over, diagnosed by a geriatrician or psychiatrist as being clinically depressed and requiring treatment. The diagnosis of depression was confirmed using the Geriatric Mental State Examination (16) and its severity corroborated by a score of 18 or more on the first 18 items of the Hamilton Rating Scale (17). None had bipolar depression.

No subjects were taking drugs known to affect protein-binding and none was on a protein-restricted or other unusual diet. All gave informed consent for a fasting uncuffed venesection taken between 6h30 and 9h30.

Results

One hundred and thirty-one non-depressed subjects (50 men) aged 17–102 (47 aged over 70 years) and 22 depressed subjects aged over 70 years (4 men) were studied.

Table II shows the results for total, free and free as a percentage of total tryptophan for non-depressed subjects. There is a statistically significant fall in total tryptophan with age. This is not accounted for by a fall in serum albumin

Table II. Plasma tryptophan levels in non-depressed and depressed subjects

		Non-depressed				
		17–69 years	70+ years	*P*	*Depressed* 70+ years	*P* 70+ *groups*
Total tryptophan						
Males:	n	32	18		4	
	Mean	14.22	12.38	<0.05	12.83	NA
	S.d.	3.77	3.52		3.58	
Females:	n	52	29		18	
	Mean	13.14	9.72	<0.001	11.87	<0.01
	S.d.	3.63	3.12		3.44	
Free tryptophan						
Males:	n	30	13		4	
	Mean	1.78	1.89	NS	2.38	NA
	S.d.	1.34	1.38		1.54	
Females:	n	49	29		18	
	Mean	1.98	2.07	NS	2.26	NS
	S.d.	1.41	1.44		1.50	
Free as percentage of total						
Males:	n	31	12		4	
	Mean	13.71	18.51	<0.001	21.5	NA
	S.d.	3.70	4.30		4.64	
Females:	n	49	29		18	
	Mean	14.78	22.29	<0.001	20.76	NS
	S.d.	3.84	4.72		4.56	

S.d.: standard deviation of mean; NS: not statistically significant; two-tailed *t* tests used. NA: statistical tests not applied.

Differences in numbers of subjects reflect laboratory errors with samples not selection of subjects.

with age [none was found in our sample since 'well elderly' were compared with 'well young' (18)].

Table II also shows that total tryptophan in subjects aged 70 years or more is statistically significantly higher in depressed females than in non-depressed females. Free tryptophan levels are higher in depressed subjects of both sexes but the differences are not significant.

Discussion

We believe that this is the largest reported sample of older subjects whose plasma tryptophan has been measured although we recognize the disadvantages of a cross-sectional study.

There are few studies of elderly subjects. Banki and Molnar (19) investigating lumbar cerebrospinal fluid amine metabolites and plasma total tryptophan found no variation with age in control subjects aged 41.5±10.7 years (but did find some decline in CSF 5-hydroxy indole acetic acid—the end product of serotonin metabolism—with age in slightly older depressed subjects). Møller et al. (20, 21) compared 87 depressed female patients (aged 52.8±17.6 years) with 60 controls

(aged 53.9±20.1 years). The controls aged over 65 were described as 'pensioners between 64 and 80 years living at home and rest home inmates between 77 and 92 years of age'. They found that the plasma tryptophan/neutral amino acid ratio declined linearly with age and that this ratio might be helpful in predicting response to antidepressive treatment.

Our finding of lower plasma total tryptophan in older subjects is hitherto unreported and is unexplained at present. The binding of tryptophan to serum albumin can be altered in several ways. Setting aside gross differences in albumin concentration (not found in these subjects) the equilibrium between 'free' and 'bound' fractions depends on the mean number of binding sites per albumin molecule and the intrinsic affinity of these sites for tryptophan. Baumann et al. (22) have suggested that more than one type of binding occurs. However, there seems to be little information concerning the relative importance of these effects and certainly none with respect to elderly subjects.

The significantly higher plasma total tryptophan in depressed elderly females and the non-significant rise in plasma free tryptophan in depressed subjects of both sexes is contrary to expectations (3) and we suspect is of no clinical importance. Unfortunately, we do not have enough data on changes in plasma tryptophan which might occur after treatment of depression. We did not estimate tryptophan/competing amino acid ratios. The value of this ratio in predicting response to anti-depressive treatment is strongly supported by some authors (e.g. 20, 21) but an earlier clinical report by De Meyer et al. (23) of a low ratio in severe depression with return to normal on resolution of the depression was not confirmed in a later study by the same authors (24).

Hitherto, there have been no reports on the effect of cuffing before venepuncture (we found no differences). Several authors do not make it clear whether fasting specimens were obtained (and at what time of day) or whether they allowed for subjects' dietary habits.

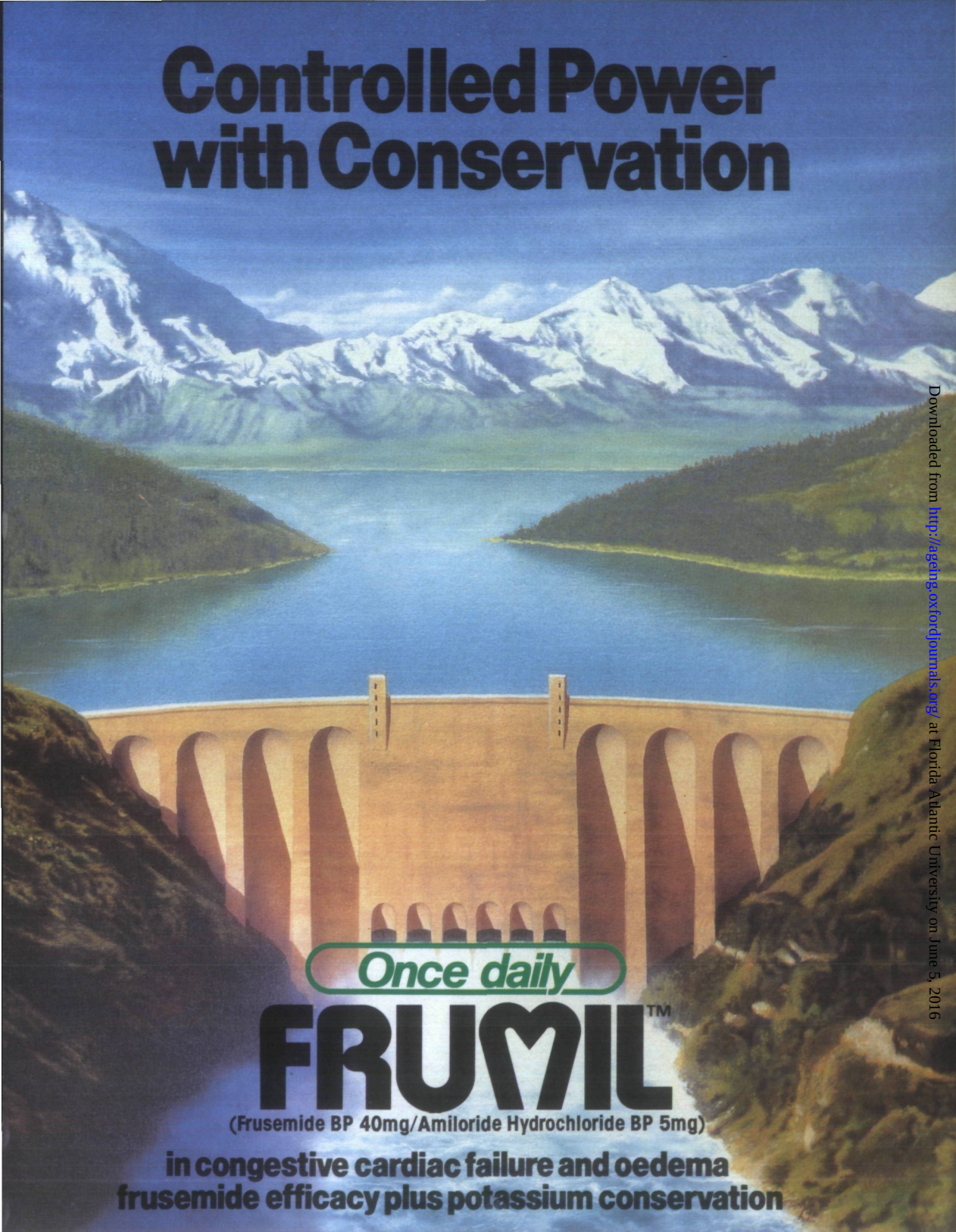
Cotlier and Sharma (25), while studying the composition of human senile cataracts, found an increase in tryptophan content and that the patients' plasma tryptophan was markedly raised. This finding was later disputed (26) but confirmed by our own work (27). This association is unexplained at present.

This study sought to remedy the paucity of information concerning variation in plasma tryptophan with age and in elderly depressed and non-depressed subjects. It was thought, somewhat simplistically, that perhaps some depression in old age might be related to low plasma free tryptophan: this assumed that depression is related to changes in serotonin metabolism and that plasma free tryptophan reflects these changes in brain neurotransmitter chemistry. In fact, no changes in plasma free tryptophan were found with age or depression.

Acknowledgements

We are indebted to our Research Assistant. Miss Cathy Chadwick, for the laboratory assays. Some of this material was first presented at the Spring Meeting of the British Geriatrics Society in Liverpool, 1983. The work was undertaken in the laboratories of Liverpool Polytechnic and was supported by Research Grant No. 354 of the Mersey Regional Health Authority.

Controlled Power with Conservation



Once daily

FRUMIL™

(Frusemide BP 40mg/Amiloride Hydrochloride BP 5mg)

in congestive cardiac failure and oedema
frusemide efficacy plus potassium conservation

ABBREVIATED PRESCRIBING INFORMATION. PRESENTATION: Orange tablets with a breakline, marked FRUMIL, each containing 40mg Frusemide B.P and 5mg Amiloride Hydrochloride B.P. **USES:** Frumil is a potassium sparing diuretic indicated for oedema, particularly in conditions where potassium conservation is important, e.g. congestive cardiac failure, nephrosis, corticosteroid therapy and oestrogen therapy, and ascites associated with cirrhosis. **DOSAGE:** Adults. One tablet each morning, increasing to two if necessary. **CONTRA-INDICATIONS:** Hyperkalaemia, concomitant potassium supplements, electrolyte imbalance, severe progressive renal disease, anuria, acute renal failure, precomatose states associated with cirrhosis, known sensitivity to frusemide or amiloride. Safety in children, or during pregnancy and lactation has not been established. **PRECAUTIONS, WARNINGS:** Diabetes, gout, renal or hepatic insufficiency, impairment of micturition, concomitant cardiac glycosides or cephaloridine therapy. Plasma potassium monitoring is recommended. The activity of antihypertensive agents may be potentiated. Hyponatraemia, hypochloraemia and raised blood urea nitrogen may occur during vigorous diuresis. **SIDE-EFFECTS:** Malaise, gastric upset, nausea, vomitting, diarrhoea and constipation may occur. Skin reactions necessitate withdrawal. Rare complications may include bone marrow depression, minor psychiatric disturbances, disturbances in liver function tests and reversible deafness. **PHARMACEUTICAL PRECAUTIONS:** Store in a cool dry place. Protect from light. **PRODUCT LICENCE NUMBER:** 0152/0183. **LEGAL CATEGORY:** POM. **PACKAGE QUANTITIES:** Cartons of 28 tablets consisting of 2 calendar foils of 14 tablets. **BNHS COST PER DAY:** 13.5p-27p.

BERK
Pharmaceuticals Ltd.
Eastbourne, England.
Glasnevin, Dublin 11.

TM Trade Mark JB800 Aug 1984

FRUMIL - A logical improvement

PARKINSON'S LORE

Titrating the dose can give you the power to relieve the 'on-off' syndrome

Conventional wisdom suggested that the 'on-off' syndrome was an unalterable feature of long-term levodopa therapy. Madopar 62.5 means that this now need not always be the case. By titrating the dose and administering more frequent, smaller doses the patient with 'on-off' syndrome and other symptoms may now obtain relief.[1]

For many patients

MADOPAR 62.5

levodopa plus benserazide

adds years to life—adds life to years

Presentation Madopar contains a combination of levodopa and the decarboxylase inhibitor benserazide in the ratio of 4:1. Madopar 62.5 capsules containing 50mg levodopa and 14.25mg benserazide hydrochloride (equivalent to 12.5mg of the base). Madopar 125 capsules containing 100mg levodopa and 28.5mg benserazide hydrochloride (equivalent to 25mg of the base). Madopar 250 capsules containing 200mg levodopa and 57mg benserazide hydrochloride (equivalent to 50mg of the base). **Indications** Parkinsonism—idiopathic, post-encephalitic. **Dosage** Dosage is variable and the data sheet should be consulted for full details. The effective daily dose usually lies between four and eight capsules of Madopar 125 (two to four capsules of Madopar 250) daily in divided doses, most patients requiring no more than six capsules of Madopar 125 daily. In some elderly patients initial treatment with one capsule of Madopar 62.5 once or twice daily, increasing by one capsule every third or fourth day, may suffice. Patients who experience fluctuations in response may also benefit from administration of smaller, more frequent doses using Madopar 62.5. **Contra-indications** Narrow-angle glaucoma, severe psychoneuroses or psychoses. Pregnancy. Patients under 25 years. It should not be given in conjunction with monoamine oxidase inhibitors or within two weeks of their withdrawal. Patients who have a history of, or who may be suffering from, a malignant melanoma. **Precautions** Drugs which interfere with central amine mechanisms should be avoided. Endocrine, renal, pulmonary or cardiovascular disease, hepatic disorder, peptic ulcer, osteoporosis, sympathomimetic drugs, antihypertensive drugs. Patients who improve on Madopar therapy should be advised to resume normal activities gradually as rapid mobilisation may increase the risk of injury. **Side-effects** Nausea and vomiting, cardiovascular disturbances, psychiatric disturbances, involuntary movements. **Package Quantities** Madopar 62.5 capsules, Madopar 125 capsules and Madopar 250 capsules in packings of 100. **Licence Numbers** 0031/0125 (Madopar 62.5 capsules). 0031/0073 (Madopar 125 capsules). 0031/0074 (Madopar 250 capsules). **Basic NHS Cost** Madopar capsules 62.5 £5.41 per 100. Madopar capsules 125 £9.76 per 100. Madopar capsules 250 £17.47 per 100.

Reference 1. Méd.et Hyg.(Genève),1981,39,3832.

Roche Products Limited, PO Box 8
Welwyn Garden City, Hertfordshire AL7 3AY

ROCHE

J522226/384

Madopar is a trade mark.

References

1. Kay DWK, Beamish P, Roth M. Old age mental disorders in Newcastle upon Tyne, Part I: A study of prevalance. *Br J Psychiatr* 1964;**110**:146–58.
2. *British Medical Journal:* Leader. Tryptophan and depression. *Br Med J* 1976;**i**:242–3.
3. Coppen A, Wood K. Tryptophan and depressive illness. *Psychol Med* 1978;**8**:49–57.
4. Fernstrom JD, Wurtman RJ. Brain serotonin content: physiological regulation by plasma neutral amino acids. *Science* 1972;**178**:414–16.
5. Tagliamonte, A, Biggio G, Vargiu L, Gessa GL. Plasma tryptophan in serum controls, brain tryptophan level and serotonin synthesis. *Life Sci* 1973;**12**:277–87.
6. Bloxham DL, Curzon G. A study of proposed determinants of brain tryptophan concentration in rats after portocaval anastomosis or sham operations. *J Neurochem* 1978;**31**:1255–63.
7. Sarna GS, Tricklebank MD, Kantamaneni BD, Hunt A, Patel AJ, Curzon G. Effect of age on variables influencing supply of tryptophan to the brain. *J Neurochem* 1982;**39**:1283–90.
8. Fernstrom JD, Hirsch MJ, Faller DV. Tryptophan concentrations in rat brain—failure to correlate with free serum tryptophan or its ratio to the sum of other serum neutral amino acids. *Biochem J* 1976;**160**:589–95.
9. Yuwiler A, Oldendorf WH, Geller E, Braun L. Effect of albumin binding and amino-acid competition on tryptophan uptake into brain. *J Neurochem* 1977;**28**:1015–23.
10. Pardridge WM. Kinetics of competitive inhibition of neutral amino acid transport across the blood–brain barrier. *J Neurochem* 1977;**28**:103–8.
11. Pardridge WM. Tryptophan transport through the blood–brain barrier: in vivo measurement of free and albumin-bound amino acids. *Life Sci* 1979;**25**:1519–28.
12. Riley GJ, Shaw DM. Total and non-bound tryptophan in unipolar illness. *Lancet* 1976;**ii**:1249.
13. Niskanen P, Huttunen M, Tamminen T, Jääskeläinen J. The daily rhythm of plasma tryptophan and tyrosine in depression. *Br J Psychiatr* 1976;**128**:67–73.
14. Curzon G, Greenwood MH. *Neuropsychopharmacology,* Amsterdam: Excerpta Medica, 1975;108–16.
15. Curzon G, Friedal J, Knott PJ. The effect of fatty acids on the binding of tryptophan to plasma protein. *Nature* 1973;**242**:198–200.
16. Copeland JRM, Kelleher MJ, Kellett JM, et al. A semi-structured clinical interview for the assessment of diagnosis and mental state in the elderly; the Geriatric Mental State Schedule. *Psychol Med* 1976;**6**:439–49.
17. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatr* 1960;**23**:56–62.
18. Caird FI. Biochemical normality in old age. In: *Advanced medicine no. 11,* London: Pitman Medical, 1975;306–16.
19. Banki CM, Molnar G. The influence of age, height and body weight on cerebrospinal fluid amine metabolites and tryptophan in women. *Biol Psychiatr* 1981;**16**:753–63.
20. Møller SE, Kirk L, Honoré P. Relationship between plasma ratio of tryptophan to competing amino acids and the response to L-tryptophan treatment in endogenously depressed patients. *J Affect Dis* 1980;**2**:47–9.
21. Møller SE, Honoré P, Larsen OB. Tryptophan and tyrosine ratios to neutral amino acids in endogenous depression. *J Affect Dis* 1983;**5**:67–9.
22. Baumann P, Duruz E, Heimann A. Determination of free and bound plasma tryptophan by ultrafiltration. *Clin Chim Acta* 1974;**1**:35–40.
23. De Meyer MK, Shea PA, Hendrie HC, Yoshimira NN. Plasma tryptophan and five other amino acids in depressed and normal subjects. *Arch Gen Psychiatr* 1981;**38**:642–6.
24. Dunlop SR, Hendrie HC, Shea PA, Brittain HM. Ratio of plasma tryptophan to five other amino acids in depressed subjects: a follow-up. *Arch Gen Psychiatr* 1983;**38**:1033–4.
25. Cotlier E, Sharma YR. Plasma tryptophan in senile cataract. *Lancet* 1980;**i**:607.
26. Allegri G, Angi MR. Free and total serum tryptophan in senile cataracts. *Lancet* 1981;**ii**:157–8.
27. Chadwick C, Phipps DA, Powell C. Serum tryptophan and cataract. *Lancet* 1981;**ii**:583.

Date accepted 5 July 1984.