TABLE II—Proportions of Patients Presenting with Erosions in First Year of Dialysis in Five Series

	No. of Patients	Proportion who Presented with Erosions	
		No.	%
Tatler <i>et al.</i> (1973)	135	16	11.9
Johnson <i>et al.</i> (1967)	33	8	24.2
Cohen <i>et al.</i> (1970)	29	6	20.7
Simpson <i>et al.</i> (1973)	11	1	9.1
Platts <i>et al.</i> (1973)	30	2	6.7
Total	238	33	13.9

TABLE III—Data as in Table II but with Patients Under 20 Years of Age Excluded*

	No. of Patients	Proportion who Presented with Erosions	
		No.	%
Tatler <i>et al.</i> (1973)	124	10	8.1
Johnson <i>et al.</i> (1967)	30	6	20.0
Cohen <i>et al.</i> (1970)	25	3	12.0
Simpson <i>et al.</i> (1973)	11	1	9.1
Platts <i>et al.</i> (1973)	28	2	7.1
Total	218	22	10.1

*Age under 20 years was associated with high incidence of erosions (see fig. 3).

giving information on erosions, however, have been assembled in table II, which shows the proportions of patients presenting with erosions in the first year of dialysis. When patients below 20 years of age are excluded (table III) the proportion presenting with erosions falls from 13.9% to 10.1%, which supports the observation that this lesion is commoner in young patients.

The results presented here call attention to the widely varying response of individual patients to renal failure and dialysis and emphasize that when comparing the results of radiological studies between different centres it will in future be essential to take into account the age and sex of the patients. Results of surveys within centres should also be evaluated with respect to the age at which dialysis was started and the average age of the group.

It now appears as a result of two different analyses that radiological bone disease in patients in this centre is indeed slowly progressive. We again emphasize, however, that bone disease is rarely symptomatic; even fractures would sometimes

have been missed had regular skeletal surveys not been performed on all patients.

Conclusions

Examination of the incidence of vascular calcification, fractures, and erosions in a cohort of patients after one and five years of dialysis has confirmed that these lesions are progressive in our patients, and this supports a concept of determining the relationship between rates of development of bone disease by comparison of the $t\frac{1}{2}$ for each lesion.

The disturbing rate of increase in lesions in patients on dialysis previously reported cannot be held to be due to dialysis alone since we have now shown that age at the onset of dialysis and to some extent sex influence the frequency with which lesions are detected. The intrinsic renal disease may also play a part in the pathogenesis of renal bone disease, as suggested by the failure of the patients with polycystic disease to develop erosions.

It now appears that the role of dialysis itself in the pathogenesis of renal bone disease cannot be determined with precision since the proportion of pre-dialysis patients with lesions has not yet been studied in detail. Preliminary studies, however, suggest that radiological changes begin to appear with rapidity in the late stages of renal failure. Whatever the effects of dialysis itself and of the therapy to mitigate or prevent the lesions it is clear that the results of intervention of any kind must be interpreted with the factors described here in mind, since bias will result from ignoring them. For example, centres which offer dialysis to children and young people will experience a different pattern of bone disease from other centres. It also seems likely that the proportion of males to females will be of importance.

References

- Cohen, M. E. L., *et al.* (1970). *Clinical Radiology*, 21, 124.
- Johnson, C., Graham, C. B., and Curtis, F. K. (1967). *American Journal of Roentgenology*, 101, 4, 915.
- Mawer, E. B., *et al.* (1973). *Lancet*, 1, 626.
- Moorhead, J. F., Baillo, R. A., and Hopewell, J. P. (1969). In *Proceedings of 4th International Congress on Nephrology*, ed. N. Alwall, F. Berglund, and B. Josephson, vol. 3, p. 131. New York, Karger.
- Platts, M. M., *et al.* (1973). *British Journal of Radiology*, 46, 585.
- Simpson, W., *et al.* (1973). *Radiology*, 107, 2, 313.
- Tatler, G. L. V., *et al.* (1973). *British Medical Journal*, 4, 315.

Combination Therapy for Myelomatosis

L. AZAM, I. W. DELAMORE

British Medical Journal, 1974, 4, 560-564

Summary

Twenty-eight patients with multiple myeloma have been treated with a quadruple chemotherapeutic regimen consisting of 1, 3 bis (2-chloroethyl)-1-nitrosourea (BCNU), cyclophosphamide, melphalan, and prednisolone. Nineteen new

patients and nine who had escaped from previous single-agent therapy were included in the study. The results to date, on eight criteria of response, seem to be superior to those obtained from previous chemotherapeutic regimens. The study has been in progress for 18 months and only three patients have died. Only one who had not received previous therapy died, and she had complicating hyperparathyroidism, which almost certainly contributed to her death.

Introduction

Over the past 10-15 years various workers have shown the ability of several alkylating agents to improve the clinical state of patients with myelomatosis, with a resultant increase

University Department of Clinical Haematology, Manchester Royal Infirmary, Manchester M13 9WL

L. AZAM, M.B., B.S., Commonwealth Postgraduate Scholar
I. W. DELAMORE, PH.D., F.R.C.P., Physician in Charge

in survival time. Response rates have been obtained in at least one index of the disease in more than 60% of patients (Liebling *et al.*, 1962; Korst *et al.*, 1964; Alexanian *et al.*, 1969; Malpas, 1969; Alexanian *et al.*, 1972; Costa *et al.*, 1973). The drug most commonly used has been melphalan, either in small doses continuously or in larger doses intermittently. It has been claimed that the response rate is better with intermittent therapy than with continuous (Alexanian *et al.*, 1969; Hoogstraten *et al.*, 1969) and that when combined with prednisolone there is a further rise in the response rate (Costa *et al.*, 1973). Trials conducted by the British Medical Research Council (1971) and the U.S. Veterans Administration (Rivers *et al.*, 1969) indicate that the therapeutic results with cyclophosphamide and melphalan are virtually identical.

Other workers have attempted to assess the effect of other drugs such as 1, 3 bis (2-chloroethyl)-1-nitrosourea (BCNU) either alone or in combination with other alkylating agents and prednisolone. The initial reports of these trials have been very encouraging (Pizzi, 1971; Harley *et al.*, 1972; Lee *et al.*, 1974), but no such study has been undertaken in the United Kingdom.

We report here our experience of a pilot study on the treatment of myelomatosis with the cyclic use of a drug combination consisting of BCNU, melphalan, cyclophosphamide, and prednisolone.

Patients and Methods

Twenty-eight patients presenting at the university department of clinical haematology, Manchester Royal Infirmary, over a period of 18 months were entered into the trial. This number included 19 consecutive previously untreated patients and nine patients who had become resistant to treatment with a single alkylating agent (usually melphalan with or without prednisolone). The untreated patients were placed in group 1 and the previously treated drug-resistant patients in group 2. Those patients who showed marked clinical deterioration and a steep rise in paraprotein production while still receiving chemotherapy were considered to be drug resistant. In some cases these changes were associated with hypercalcaemia, azotaemia, and anaemia. The types of myeloma present in these patients are shown in table 1.

The therapeutic regimen used was as follows: day 1, BCNU 75 mg/m² intravenously; days 1-7, melphalan 2 mg/day by mouth; days 1-14, cyclophosphamide 50 mg/day and prednisolone 40 mg/day by mouth. The course was repeated every eight weeks—that is, with an interval of six weeks free of treatment. It was decided to continue treatment until the

paraprotein band on electrophoresis had disappeared and the patient was in complete remission.

Subjective Response.—The performance status of each patient was classified according to the following scoring system adapted from *Cancer Chemotherapy Reports* (1968, 1973): 0 = no evidence of disease; 1 = symptomatic but able to continue with normal work and activity; 2 = too ill to work but less than 50% of the time spent in bed; 3 = too ill to work and more than 50% of the time spent in bed; and 4 = severely disabled and in need of hospital treatment and active supportive therapy.

Objective Response.—Each patient was considered to have achieved an objective response to treatment if the following criteria were fulfilled: (a) the produce of the two largest diameters of palpable or x-ray visualized plasmocytomas regressed 50% or more; (b) the serum myeloma globulin level decreased 50% or more and to less than 4 g/100 ml; (c) urinary light chain excretion reduced to 50% or less of the pre-treatment values; (d) the haemoglobin level was maintained above 9 g/100 ml; (e) serum albumin level was maintained above 3 g/100 ml; (f) serum calcium level was maintained below 10-10.5 mg/100 ml; (g) bone marrow myeloma cell infiltration was reduced to below 5% of the total nucleated cells; (h) adequate renal function was maintained, as measured by blood urea levels, creatine clearances, and urinary albumin output.

Results

SUBJECTIVE RESPONSE

The subjective response of patients in group 1 was measured by the performance status scoring system (table II). Ten patients were severely disabled and bedridden before therapy began, four were too ill to work, and five were symptomatic, mostly complaining of severe backache, but were able to continue with their normal work. After a single course of chemotherapy five patients became completely asymptomatic and only one patient was still severely disabled. She had associated primary hyperparathyroidism and nephrocalcinosis, which almost certainly contributed to her clinical deterioration and eventual death. All patients who received more than five courses of therapy were asymptomatic.

In group 2 eight patients were in the severely disabled group and one patient, though he could look after himself, was unable to work and spent more than 50% of his time in bed. After one course of chemotherapy four patients were asymptomatic and three were able to go about their normal work though still symptomatic; two were still too ill to work but were able to look after themselves. One patient de-

TABLE 1—Types of Myeloma Protein Present in 28 Patients in Two Groups

	IgG ₁	IgG ₂	IgG ₃	IgG ₄	IgA	Light-chain Myeloma	Non-secretory Myeloma	Light-chain Type	
								κ	λ
Group 1	6	3	4	3	2	1	1	10	9
Group 2	1	3	1		3			3	5

TABLE II—Performance Status (on Scale from 0-4) of Patients Before and During Treatment

No. of Courses of Treatment Given	Group 1						Group 2					
	No. of Patients Tested	No. of Patients in Clinical Category:					No. of Patients Tested	No. of Patients in Clinical Category:				
		0	1	2	3	4		0	1	2	3	4
0	19		5	1	3	10	9				1	8
1	19	5	8	4	1	1	9	4	3	2		
2	15	8	7				4	1	2	1		
3	8	6	2				3		2	1		
4	7	6	1				1		2			
5	4	3	1						1			
6	2	2										
7	1	1										
8	1	1										

teriorated, both subjectively and objectively, after an initial response and died soon afterwards. This group was less predictable than group 1, but all patients showed some response unless other disease processes were present.

OBJECTIVE RESPONSE

Plasmocytomas.—The regression of plasmocytomas could not be properly evaluated because the follow-up period was too short. In three patients in group 1 who were reassessed after one year, however, there was remarkable improvement in the radiological bone density, and in one there was marginal osteosclerotic healing of previously well-defined lytic areas. Two patients with extramedullary masses showed total regression after one course of therapy.

Serum Paraprotein Levels.—Five patients could not be evaluated because one had a non-secretory myeloma and the others had a total globulin of less than 4 g/100 ml. A 50% or more decrease in the serum paraprotein level and a reduction in total globulins to less than 4 g/100 ml was used as the second criteria. There was a better response in group 1 than in group 2, but there was a significant reduction in both groups (table III). After the first course of therapy 62.5% of group 1 responded. This percentage increased after subsequent courses. Only one patient who had more than five courses of therapy failed to show a reduction below 50% of the pretreatment value. In group 2 no patient showed a response after one course of treatment, but after two courses three out of five did so. The response was maintained less well, and after five courses the percentage of patients maintaining a significant drop in the immunoglobulin level was reduced. The synthetic index for each of these patients was calculated according to the method described by Salmon (1973). All patients in group 1 showed a significant reduction of the synthetic index, and a reduction to less than 50% of the pretreatment value occurred in 13 patients after a single course of chemotherapy and to less than 25% in six patients after further treatment (fig. 1). The reduction of the synthetic index was well maintained in all patients. There was also a reduction in all patients in group 2 though it was less well maintained (fig. 2). Four patients showed a reduction to less than 50% of their pretreatment values after a single course of chemotherapy, but in only one patient was the level reduced to less than 25%.

Urinary Light Chain Excretion.—All but four patients in group 1 and two patients in group 2 had Bence-Jones proteinuria. In group 1 there was a significant response in 80% of patients after one course of therapy (table III). No patient who had five courses or more still had Bence-Jones protein in the urine. Good results were also obtained in patients in group 2. After five courses of therapy detectable urinary light chains were present in only two patients, and in one of these they disappeared after eight courses.

Haemoglobin Level.—In group 1 all but three patients had an initial haemoglobin level above 9 g/100 ml and in all

FIG. 1—Position on synthetic index for paraprotein plotted against number of courses received in group 1.

FIG. 2—Position on synthetic index for paraprotein plotted against number of courses received in group 2.

three it rose above that level. One patient died after only one course of therapy and the other two required blood transfusions, but as treatment progressed no further blood transfusions were required and the haemoglobin level continued to rise. The haemoglobin level was initially below 9 g/100 ml in six patients in group 2. In two of them there was a rise to above 9 g/100 ml after one course of therapy. Two more were

TABLE III—Paraprotein Response in Blood and Urine in Two Groups of Patients

No. of Courses of Treatment Given:	1	2	3	4	5	6	7
Blood							
Group 1: No. of patients tested	16	11	8	7	4	2	2
No. (%) responding*	10 (62.5)	8 (72.7)	6 (75.0)	5 (71.4)	3 (75.0)	2 (100)	2 (100)
Group 2: No. of patients tested	7	5	4	2	1	1	
No. (%) responding*	0	3 (60)	1 (25)	1 (50)	1 (100)	1 (100)	
Urine							
Group 1: No. of patients tested	15	8	5	2			
No. (%) responding†	12 (80)	8 (100)	5 (100)	2 (100)			
Group 2: No. of patients tested	9	7	4	3			
No. (%) responding†	9 (100)	7 (100)	4 (100)	3 (100)			

*A patient achieved objective response if serum myeloma globulins reduced to less than 50% of pretreatment level and to less than 4 g/100 ml.

†A patient achieved objective response if urinary light chains were reduced to less than 50% of pretreatment values.

given blood transfusions, but in all cases the haemoglobin level showed an upward trend after chemotherapy except in one patient.

Serum Albumin Levels.—In group 1 the serum albumin level was below 3 g/100 ml in four patients. In two of these the level rose to above 3 g/100 ml after one and four courses of treatment. In one patient there was a further fall after one course of treatment. This was the patient who subsequently died. In one other patient the level rose but we had, at the time of writing, given only two courses of treatment and the level, while still rising, had not yet reached 3 g/100 ml. In two patients in whom the level was above 3 g/100 ml before treatment began there was a fall to below that figure after one course of treatment. One patient died at this point, but in the other the level rose again to above 3 g/100 ml after a further course of therapy and was maintained. In group 2 five patients had a serum albumin level below 3 g/100 ml before treatment began. In four of them the level rose after one or two courses of treatment to above 3 g/100 ml. In the fifth patient it continued to fall, and the patient died after the first course of therapy.

Serum Calcium Levels.—These were measured and corrected for the corresponding serum protein levels. Only two patients in group 1 had a high level of serum calcium, and in both there was a prompt fall to within normal limits after chemotherapy. Only one patient in group 2 showed a high level of serum calcium. He also had a prompt response to treatment. All of these patients had been treated with rehydration and steroids with no significant effect on their high serum calcium levels before chemotherapy.

Myeloma Cell Infiltration of Bone Marrow.—The criteria for response here was a reduction of bone marrow cells to below 5% of the total nucleated cells. In both groups this response was shown by over 80% of patients. In the remaining patients in both groups there was a marked reduction in the plasma cell infiltration, but there were some residual clumps of myeloma cells, and we did not include them as having shown a significant response.

Renal Function.—This was assessed by monitoring the blood urea level, creatinine clearance, urinary albumin, and the differential clearance of low molecular weight proteins. Three patients in group 1 had gross renal impairment with a raised blood urea and a greatly impaired creatinine clearance. All three responded with a reduction in the blood urea concentration and an improved creatinine clearance, but in all three the response was considered to be incomplete and the blood urea levels did not return to normal. In group 2 five patients had initially raised blood urea levels with an associated impairment of creatinine clearance. There was some response in every case and in two patients the blood urea was maintained below 40 mg/100 ml. In one there was an initial fall in the blood urea concentration and an improved creatinine clearance, but he subsequently deteriorated, the blood urea rising to about 200 mg/100 ml before he died. In group 1 five patients had a urinary albumin excretion above 2 g/24 hours. This slowly fell after treatment but in no cases did it completely disappear. All five patients had an associated Bence-Jones proteinuria, which disappeared completely with therapy in every case. In group 2 there were also five patients with albuminuria, but only three had an excretion level above 2 g/24 hours. All five had Bence-Jones proteinuria. In four patients the urinary albumin level fell sharply after the first course of treatment, but it never completely disappeared though in one patient it fell to less than 100 mg/24 hours. The Bence-Jones protein disappeared in every case except one.

SURVIVAL

This study had been in progress for 18 months at the time of writing, but many patients were under observation for a

shorter period. It is therefore impossible to make any meaningful statement about survival time. Only one patient in group 1 died. This patient had primary hyperparathyroidism in addition to her myeloma and she died in renal failure. Two of the nine patients in group 2 died. One patient was in renal failure and had a pancytopenia before treatment when the drug combination was begun. Before he died in severe renal failure with a subdural haemorrhage only one course of therapy had been given. The second patient initially responded to treatment and was once again able to lead an active life for 15 months while receiving the combination therapy.

Discussion

The simultaneous use of one or more alkylating agents for the treatment of myeloma has not been extensively investigated. Some workers believe that when myeloma fails to respond to one alkylating agent it will not respond to a second because of the existence of cross resistance. Other workers deny the existence of cross resistance, and Wheeler (1963) claims that even if cross resistance does exist it does not indicate that the drugs have a common mode of action. He points out that two alkylating agents might have different specific sites of action that cause their particular biological effects but, nevertheless, be prevented from reaching those sites by a common mechanism such as reduced membrane permeability or detoxification. Moreover, there is some evidence that alkylating agents may have a synergistic effect (DeVita and Schein, 1973). It was therefore decided to use three alkylating agents simultaneously and to augment their effects by prednisolone. The three agents chosen were ones which were known to produce beneficial effects in myeloma, and prednisolone was used because it has been claimed to potentiate the action of each of the drugs when used with them. We were further encouraged to use combination chemotherapy by the results of cell culture studies carried out on seven of our patients (to be published elsewhere).

On most criteria a very high response rate was achieved if enough courses of treatment were given. The results seem to be better than those obtained with the use of a single agent only. The regimen used by Harley *et al.* (1972) on behalf of leukaemia group B in the U.S.A. used oral melphalan in a dose of 8 mg/m² together with cyclophosphamide 300 mg/m² intravenously and BCNU 100 mg/m² intravenously all on day 1. Prednisolone was given in a dose of 1.2 mg/kg/day for two weeks and gradually tailed-off over the next four weeks. Our regimen used larger doses of melphalan and cyclophosphamide, but the drugs were spread out over a longer period and we used cyclophosphamide orally instead of intravenously.

Three points in particular about the regimen should be emphasized. Firstly, we found it easy to administer and remarkably free from side effects with a notable absence of gastrointestinal disturbance and bone marrow suppression in previously untreated patients. Secondly, we believe that the use of this regimen has saved some patients who would have died if single-agent therapy had been used. This applies particularly to patients who had a high blood urea level and were very ill when first seen. It was also most effective in some patients who had escaped from single-agent therapy. Thirdly, we believe it to be more effective in reducing the level of paraprotein than previous forms of treatment. Every patient showed some response in the paraprotein level, in contrast to results with previous regimens using single-agent chemotherapy with or without the addition of prednisolone. In the best of such series 30% or more of patients showed no response whatsoever. Since this paper was prepared three patients have shown complete disappearance of detectable paraprotein, and can be said to be

in clinical and biochemical remission with some evidence of osteosclerotic healing of the lytic areas of bone. This is usually associated with a very good prognosis.

Of the four agents used in this regimen, BCNU is most effective. It may well be that other nitrosourea compounds are equally effective, and future trials with CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) and methyl-CCNU, in combination with other alkylating agents, should be undertaken.

We thank Dr. A. Gowenlock and his staff in the clinical laboratories, Manchester Royal Infirmary, and Dr. H. MacFarlane and his staff in the biochemistry department of the University of Manchester for their excellent laboratory support. We also thank Dr. Roy Jefferis of the University of Birmingham for IgG subclass typing.

We are greatly indebted to the National Cancer Institute, Bethesda, Maryland, U.S.A., for the supply of BCNU. One of us (L.A.) is in receipt of a Commonwealth Scholarship.

References

- Alexanian, R., *et al.* (1969). *Journal of the American Medical Association*, **208**, 1680.
 Alexanian, R., *et al.* (1972). *Cancer*, **30**, 382.
 Costa, G., *et al.* (1973). *The American Journal of Medicine*, **54**, 589.
 DeVita, V. T., and Schein, P. S. (1973). *New England Journal of Medicine*, **288**, 998.
 Harley, J. B., *et al.* (1972). *The West Virginia Medical Journal*, **68**, 1.
 Hobbs, J. R. (1969). *British Journal of Haematology*, **16**, 599.
 Hoogstraten, B., *et al.* (1969). *Journal of the American Medical Association*, **209**, 251.
 Korst, D. R., *et al.* (1964). *Journal of the American Medical Association*, **189**, 758.
 Lee, B. J., *et al.* (1974). *Cancer*, **33**, 533.
 Liebling, M., *et al.* (1962). *Cancer Chemotherapy Report*, **16**, 253.
 Malpas, J. S. (1969). *British Medical Journal*, **2**, 163.
 Medical Research Council. (1971). *British Medical Journal*, **1**, 640.
 Pizzi, G. B. (1971). In *Proceedings of a Seminar in Clinical Oncology*, p. 23. Padova, Piccin Medical Books.
Cancer Chemotherapy Report, part 2. (1968). **1**, 17.
Cancer Chemotherapy Report, part 3. (1973). **4**, 145.
 Rivers, S. L., and Patno, M. E. (1969). *Journal of the American Medical Association*, **207**, 1328.
 Salmon, S. E. (1973). *Seminars in Hematology*, **10**, 135.
 Wheeler, G. P. (1963). *Cancer Research*, **23**, 1334.

Plasma Tryptophan and Sleep

C. N. CHEN, R. S. KALUCY, M. K. HARTMANN, J. H. LACEY, A. H. CRISP, J. E. BAILEY, E. G. ECCLESTON, A. COPPEN

British Medical Journal, 1974, **4**, 564-566

Summary

Free, bound, and total plasma tryptophan (F.P.T., B.P.T., and T.P.T.) levels have been measured throughout the night in six young female volunteers. All-night polygraphic sleep recordings were also made. No direct temporal relationship was found between plasma tryptophan levels and specific sleep stages. The mean F.P.T. levels, however, were found to have a positive correlation with rapid-eye-movement (R.E.M.) sleep and a negative correlation with non-R.E.M. sleep. An inverse relationship existed between the F.P.T. and B.P.T. levels. There appeared to be a diurnal variation in F.P.T. levels, with high readings in the first half of the night.

Introduction

Animal experiments by Jouvet *et al.* (1967) have shown that 5-hydroxytryptamine (5-HT) may mediate slow-wave sleep and noradrenaline rapid-eye-movement (R.E.M.) sleep. Human experiments, however, have yielded discrepant findings. An increase in R.E.M. sleep has, in fact, been shown to occur after

intravenous injection of 5-hydroxytryptophan (Mandell *et al.*, 1965) and oral doses of tryptophan (Hartmann, 1967) in normal adults. Oswald *et al.* (1964) reported that oral administration of tryptophan reduced R.E.M. latency. When parachlorophenylalanine was used to suppress the synthesis of 5-HT R.E.M. sleep was reduced (Wyatt *et al.*, 1969). Nevertheless, tryptophan was also found to enhance total sleep time, non-R.E.M. sleep, and delta-wave sleep, suggesting that tryptophan and 5-HT may have different effects on sleep (Wyatt *et al.*, 1970). It is difficult to reconcile these findings when attempting to relate specific monoamines to changes in sleep stages.

Normally about 90% of the total plasma tryptophan (T.P.T.) is bound to albumin (B.P.T.) and the remaining plasma tryptophan is present in the free fraction (F.P.T.). It has been shown that the F.P.T. levels may directly affect the brain tryptophan levels, which would lead to an increase in the rate of turnover (Tagliamonte *et al.*, 1971 a; Knott and Curzon, 1972) or in the amount of brain 5-HT (Moir and Eccleston, 1968; Wurtman and Fernstrom, 1972). A technique for estimating F.P.T., B.P.T., and T.P.T. has been developed (Eccleston, 1973). We report here the results of a preliminary investigation on the relationship between plasma tryptophan (F.P.T. and B.P.T.) levels and electroencephalographic sleep in normal young women.

Method

After one adaptation night polygraphic sleep recordings were taken between 11 p.m. and 7 a.m. from six young, healthy female volunteers. Standard sleep electroencephalographic techniques (Rechtschaffen and Kales, 1968) were adopted. All records were scored by an independent observer. Blood samples were collected by means of an indwelling cannula. The procedure for the estimation of F.P.T., B.P.T., and T.P.T. was the same as that described elsewhere (Coppin *et al.*, 1973). The plasma samples were numbered at random and the code was not broken until all the samples had been estimated. Diet was controlled on the day before blood collection.

Academic Department of Psychiatry, St. George's Hospital Medical School, London S.W.17

C. N. CHEN, M.B., M.R.C.PSYCH., Research Fellow
 R. S. KALUCY, F.R.C.P., M.R.C.PSYCH., Research Fellow
 M. K. HARTMANN, B.A., Research Assistant
 J. H. LACEY, M.B., M.R.C.PSYCH., Research Fellow
 A. H. CRISP, F.R.C.P., F.R.C.PSYCH., Professor

Medical Research Council Neuropsychiatry Laboratory, West Park Hospital, Epsom, Surrey

J. E. BAILEY, R.M.N., Research Assistant
 E. G. ECCLESTON, F.I.M.L.T., Research Biochemist
 A. COPPEN, M.D., F.R.C.PSYCH., Director