At present methods of classifying and quantifying disability vary so much from centre to centre that it is difficult if not impossible to draw valid conclusions from any comparison between differing methods of rehabilitation. The methods used in rehabilitation also tend to be based more on ill-defined concepts of the virtue of exercise and example rather than validated methods of dealing with specific problems. It is extremely difficult to quantify rehabilitation methods in the same way as the dose of a drug is quantified. The response to these methods also varies from individual to individual, and certainly may contain a large placebo effect. It seems then that as a scientific discipline rehabilitation has hardly established its terms of reference and has not yet defined its units of measurement.

There have been a few notable studies in this field. The work of Copp in Manchester,[1] Ferguson and MacPhail in Glasgow,[2] and the multicentre trials of the British Association of Physical Medicine and Rheumatology spring to mind, but surely before implementing the recommendations of the Tunbridge report[3] it is essential that basic studies should be carried out first by expanded academic departments of rehabilitation medicine, preferably organized on a regional basis, so that the degree and nature of the problems throughout Britain can be adequately defined and subsequently dealt with.—I am, etc.,

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Periodicity of Serum Prolactin Concentration

SIR,—Using a sensitive, precise, and specific radioimmunoassay for thyroid stimulating hormone (TSH) and a continuous blood sampling technique we have recently demonstrated the existence of a circadian rhythm of TSH concentration in peripheral blood in man.[1 2] Our findings have confirmed the extensive observations of Nicoloff[3] who obtained indirect evidence for fluctuations in thyrotrophic activity over the 24-hour period by using thyroidal iodine release measurements.

When synthetic thyrotrophin releasing hormone (TRH) was shown to be a potent stimulator of prolactin release as well as of TSH,[4] the obvious question was raised whether these two pituitary hormones had a common hypothalamic releasing hormone under physiological conditions. We therefore note with considerable interest the report by Dr. J. Nokin and his colleagues (2 September, p. 561) of a circadian rhythm of serum prolactin concentrations in men and non-pregnant women, with peak levels occurring between 1 a.m. and 5 a.m. This pattern bears a striking resemblance to the circadian rhythm of plasma thyrotrophin previously reported by our group.[1] It strongly favours a common releasing hormone for prolactin and TSH and supports the suggestion of Bowers[5] that TRH should be renamed PTRH (prolactin-thyrotrophin releasing hormone).

Three additional points deserve comment. Firstly, the question of the physiological role of the prolactin inhibitory hormone has been highlighted by these findings. Secondly, in our studies of seven men and four women the basic circadian pattern of TSH has been similar in the two sexes. Finally, it is now becoming increasingly apparent that the plasma concentrations of several hormones —for example, cortisol[6] and luteinizing hormone[7] fluctuate widely over very short time intervals, suggesting episodic secretion. Consequently, intermittent blood sampling techniques fail to characterize adequately the total 24-hour pattern of circulating hormone concentrations, especially if sampling is infrequent, such as the four-hourly intervals employed by Dr. Nokin and colleagues. Our own recent evidence derived from blood samples collected continuously and integrated over 20- or 40-minute periods for 12 hours overnight in four healthy adults (two men and two non-pregnant women) and for 48 hours in one healthy male demonstrates that additional short-term variations of thyrotrophin levels occur superimposed on the circadian rhythm. The magnitude and pattern of these variations is such that periodic secretion of thyrotrophin seems the most likely explanation. Clearly, the simultaneous measurement of TSH and prolactin using very short sampling times or a continuous sampling technique or both are necessary to define more precisely the relationship between their daily secretory patterns and the physiological role of their possible common releasing hormone.—We are, etc.,

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Propranolol and Cluster Headache

SIR,—A report of favourable results in treating severe cluster headache in a 30-year-old man with propranolol may be of interest.

The patient had suffered for 10 years from recurring attacks of right-sided, throbbing headache lasting about 1-2 hours. During the two months before hospitalization the attacks had increased in frequency, occurring many times daily, and the patient had been almost unable to sleep. The attacks always began on the right side of the neck and spread up to the right side of the head, with maximum intensity in and around the eye. Often the pain was felt in the right shoulder and upper chest. During an attack the right eye wept, there was some photophobia, and the right temporal artery was swollen and tender. The attacks were never accompanied by visual disturbances but sometimes by nausea and vomiting. There was no family history of headache. Clinical examination and laboratory tests were normal. Many treatments had been given, including ergot and dihydroergot preparations, prochlorperazine, corticosteroids, various kinds of analgesics, and carbamazepine, without any discernible effects.

During the first week of hospitalization the patient continued to have many attacks despite various analgesics. Treatment with propranolol was begun in the second week with a dose of 60 mg/day for two days and then 80 mg/day for another three days. After one day's medication the patient became completely symptomless and remained so for one week after stopping propranolol. Then mild symptoms returned, which ceased promptly after instituting propranolol 60 mg/day.

The type of headache described fits well with the criteria of so-called cluster or histamine headache.[1] Recently promising results from treating migraine with propranolol have been reported,[2] but so far as I know there are no reports of the effects of propranolol on cluster headache. The mechanism is open to discussion, but one might assume that the inhibitory effect of propranolol on histamine activity, demonstrated in relation to gastric acid secretion,[3] might also be the mechanism of its effect on cluster headache. The favourable result in this one case seems to warrant further trials. —I am, etc.,

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Occupational Exposure to Nalidixic Acid

SIR,—A case of severe haemolytic anaemia in a breast-fed baby whose mother had been treated for pyelonephritis with nalidixic acid has been reported.[1] After recovery the infant's erythrocyte glucose-6-phosphate dehydrogenase (G-6-PD) was found to be normal. Another case of acute haemolytic anaemia in a baby after 48 hours' treatment with nalidixic acid has also been reported.[2] This baby has pronounced erythrocyte G-6-PD deficiency. We report here a case of haemolytic crisis in a man aged 20 who was exposed to nalidixic acid in his work in the pharmaceutical industry. He had no previous history of illness of any importance.

On 17 and 18 January 1972 the man's work consisted in pouring nalidixic acid dust into a large container with a small shovel three to four times a day. His working area had no extractor-fan ventilation and the process raised a very fine dust clearly visible to the naked eye. In the evening of 18 January he began to suffer from acute asthenia, anorexia, hyperpyrexia, and his urine became dark. He did not return to work but the symptoms improved during the next three days. When seen by us on 21 January his general condition was fairly good, the sclerae were jaundiced, and there was slight enlargement of the spleen. Investigation showed Hb 12 g/100ml; R.B.C. 3,800.000/mm^3; leucocytes were within normal limits; a blood smear showed slight anisocytosis, no poikilocytes, no target cells, and no nucleated red cells. P.C.V. 34%, reticulocytes 25%. The urine was strongly hyperchromatic and contained much urobilin but no biliary pigments. Total serum bilirubin was 1·50 mg/100 ml and the indirect 1 mg/100 ml; serum transaminase and alkaline phosphatase were normal. Haemoglobin electrophoresis was normal and the HbA_2 was within normal limits. The fetal Hb was normal, and the direct

Coombs test negative. There was a gross deficiency of erythrocyte G-6-PD. The patient was transferred to another job. After a month the blood findings had returned practically to normal; the urine contained no urobilin; and the serum bilirubin was 0·5 mg/100 ml.

We believe that the acute haemolytic crisis in this patient was due to nalidixic acid. The patient had not eaten broad beans nor taken any haemolysing drugs, nor had he come into contact with any other haemolysing substances in his work. We record this case to draw attention to the importance of G-6-PD-screening in subjects who are occupationally exposed to nalidixic acid or other haemolysing drugs.—We are, etc.,

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1 Belton, E. Margaret, and Vaughan Jones, R., *Lancet*, 1965, **2**, 691.
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E.B. Virus and Multiple Sclerosis

SIR,—The hypothesis that multiple sclerosis is a late manifestation of an infectious disease common in childhood was introduced by Poskanzer and colleagues.[1] Since then more than 30 virus antigens have been used to test antibodies in serum specimens from patients with multiple sclerosis and control subjects. Many studies have indicated that antibodies to measles virus are slightly but consistently raised in patients with multiple sclerosis compared with controls. The hypothesis implies that all viruses are suspected if they are able to cause persistent cell infection and can penetrate the central nervous system.

Epstein-Barr virus is known to cause relatively mild infections in children[2] and infectious mononucleosis in adolescents[3] sometimes complicated by inflammation of the central nervous system.[4] E.B. virus antibodies have not been studied earlier in this connexion. We therefore compared the titres of E.B. virus antibodies in serum specimens from 52 patients with multiple sclerosis, from 39 of their siblings, and from 52 carefully selected controls matched for age, sex, and place of residence to reveal the possible differences in antibody levels between the groups. Antibody titres to herpes simplex, varicella-zoster, and measles virus were also included in the results.

Antibodies to E.B. virus were tested by Henle's indirect immunofluorescence technique.[5] Complement fixing antibodies to other herpesviruses and haemagglutinating antibodies to measles virus were tested as described.[6] The results expressed as mean titres are shown in the Table.

Test	Geometric Mean		
	Multiple Sclerosis	Siblings	Controls
Measles H.I. ..	38·4*	28·8	26·7
Herpes C.F. ..	23·6	30·4	18·0
Zoster C.F. ..	4·2	4·4	4·2
E.B.V. F.A. ..	187·2	175·7	186·6

* The difference compared with the controls is statistically significant ($P < 0.05$)

The only statistically significant difference is seen in the measles H.I. test. The results do not indicate any connexion between the herpesviruses, including E.B. virus, and multiple sclerosis.—We are, etc.,

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1 Poskanzer, D. C., Schapira, K., and Miller, H., *Lancet*, 1963, **2**, 917.
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Source of Contamination in Haemodialysis Equipment

SIR,—We wish to report a potential source of bacterial contamination in haemodialysis equipment using an external electrolyte standard. This was discovered while investigating a patient on intermittent haemodialysis who became pyrexial towards the end of each dialysis. Repeated blood cultures were sterile but *Pseudomonas aeruginosa* and *Alcaligenes sp.* were isolated from the dialysate entering the dialyser. The dialysate was supplied from a Lucas proportionating system which was disinfected between dialyses with formalin. Dialysate taken from the header tank contained both organisms but they were not isolated from the water or the concentrated dialysate supply. The organisms were also isolated from the external electrolyte standard which surrounds an electrode and is contained in a test-tube suspended in the header tank. When the test-tube is emptied or filled the electrode is frequently placed directly in the header tank, a procedure that would permit transfer of micro-organisms.

The electrolyte standard was prepared in the chemical pathology department using glucose-free concentrated dialysate and deionized water and was distributed in 500-ml glass-stoppered stock bottles. *Ps. aeruginosa* and *Alcaligenes sp.* were isolated from the electrolyte standard stock bottle of the patient under investigation and of another symptomless patient. All the strains of *Ps. aeruginosa* were indistinguishable by pyocine typing.

These findings suggest that the dialysate in the header tank became contaminated by the electrolyte standard solution. The standard is now distributed in 1-oz (28-ml) universal bottles and autoclaved before use.—We are, etc.,

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Interaction of Benzodiazepines with Tricyclic Antidepressants

SIR,—We were interested that Dr. M. Orme and others (9 September, p. 611) found that benzodiazepine drugs had no significant effect on plasma levels of warfarin. Their findings are pertinent to a study we have just completed to investigate possible interactions between various tranquillizing and hypnotic drugs and the steady-state plasma levels of tricyclic antidepressants. Twelve psychiatric patients were studied and in none could we detect a significant alteration in the plasma level of nortriptyline attributable to benzodiazepine drugs. The drugs given were nitrazepam, chlordiazepoxide, diazepam, and oxazepam.

We did, however, demonstrate a lowering of plasma nortriptyline level in a smaller number of patients who were given amylobarbitone. This is in accord with earlier work showing that barbiturates induce hydroxylating enzymes causing increased metabolism of tricyclic drugs and resultant lowering of the steady state level.[1 2]

We obtained puzzling results in a small number of patients who were given benzoctamine. The studies were too few to be more than only suggestive at this stage of a possible complex interaction. We feel that our results reinforce the conclusion of Dr. Orme and his colleagues that benzodiazepine drugs in man are remarkably free from interaction effects. We feel therefore that when anxiolytics are necessary in addition to tricyclic antidepressants they should be of this group and that nitrazepam should be the hypnotic of choice, particularly in depressed patients.—We are, etc.,

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1 Hammer, W., Idestrôm, C. M., and Sjöqvist, F., in *Antidepressant Drugs*, ed. S. Garattini and M. N. G. Dukes, p. 301. Amsterdam, Excerpta Medica, 1967.
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Nutritional Rickets in Immigrants

SIR,—Dr. J. A. Ford and others (19 August, p. 446) have drawn our attention to a situation which has concerned us for some time. We disagree with their conclusions that the high phytate content of unleavened bread is the major cause of late rickets and osteomalacia in Pakistani and Indian communities in Glasgow. They did not mention any of the well-established criteria for the diagnosis of osteomalacia such as clinical features, discovery of vitamin D and calcium deficiency in the diet, radiological and histological findings, and the exclusion of renal disease or malabsorption by appropriate tests. The serum calcium was not corrected to its protein concentration and there was no mention of serum alkaline phosphatase in healthy children of comparable age. Part of the rise in the serum alkaline phosphatase in their children could have been due to the pubertal spurt of growth.[1]

Clearly calcium and phosphorus balance investigations would be necessary to determine the response to a chupatty-free diet and to implicate phytates in the aetiology of osteomalacia. Failing those, estimation of urinary calcium and total hydroxyproline excretion and data on the growth of these children during seven weeks' treatment would have provided some useful indication of healing bone disease. The authors do not mention low intake of calcium through the soft drinking water in Glasgow, which could be of significance in immigrant children with