superinfection by *Mycobacterium tuberculosis*. A repeat chest radiograph taken three months later would have been a wise precaution. In the event both doctors were discovered to have active disease six months later.

Compared with other hospital workers, doctors are the least compliant in caring for themselves; those at greatest risk are pathology staff who handle infected specimens.[25] They do not—though some would like to believe it—possess divine immunity from all ills, and it is in their own interest as well as that of their colleagues and patients to present for preventive examination. A well coordinated occupational health service in the NHS is overdue.[26]

FREDA FESTENSTEIN

Assistant Chest Physician,
London Chest Hospital,
London E2 9JX

1 Anonymous. Awareness of tuberculosis [Editorial]. *Br Med J* 1973;i:308.
2 Springett VH. Tuberculosis—epidemiology in England and Wales. *Br Med J* 1972;i:422-3.
3 Grange JM. The changing tubercle. *Br J Hosp Med* 1979;**22**:540-8.
4 McCarthy OR. Asian immigrant tuberculosis—the effect of visiting Asia. *Br J Dis Chest* 1984;**78**: 248-53.
5 Caplin M, Rehahn M. *Alcoholism and tuberculosis*. Tunbridge Wells: Pitman Medical, 1978. (Topics in Therapeutics No 4.)
6 British Thoracic and Tuberculosis Association. A survey of tuberculosis mortality in England and Wales in 1968. *Tubercle* 1971;52:1-2.
7 Anonymous. Deaths from tuberculosis [Editorial]. *Br Med J* 1971;ii:419.
8 Anonymous. Tuberculosis mortality under scrutiny [Editorial]. *Lancet* 1971;i:1167-8.
9 Horne NW. Problems of tuberculosis in decline [Editorial]. *Br Med J* 1984;**288**:1249-51.
10 Anonymous. Tuberculosis in hospital staff [Editorial]. *Lancet* 1973;i:525-6.
11 Ashley MJ, Wigle WD. The epidemiology of active tuberculosis in hospital employees in Ontario, 1966-1969. *Am Rev Respir Dis* 1971;**104**:851-60.
12 Barrett-Connor E. The epidemiology of tuberculosis in physicians. *JAMA* 1979;**241**:33-8.
13 Poole G. Tuberculin sensitivity and tuberculosis in 1779 nurses. *British Journal of Tuberculosis and Diseases of the Chest* 1954;**48**:230-7.
14 Simmonds FAH. *The protection of the nurse against tuberculosis*. London: National Association for the Prevention of Tuberculosis, 1952.
15 Stewart CJ. Tuberculosis infection in a paediatric department. *Br Med J* 1976;i:30-2.
16 Belfield PW, Arnold AG, Williams SE, Bostock AD, Cooke NJ. Recent experience of tuberculosis in junior hospital doctors in Leeds and Bradford. *Br J Dis Chest* 1984;**78**:313-6.
17 Ministry of Health. *Prevention of tuberculosis among hospital staff*. London: NHS, 1961. (Health Circular HM(61)84.)
18 Department of Health and Social Security. *Health services management control of tuberculosis in NHS employees*. London: DHSS, 1978. (Health Circular HC(78)3.)
19 Joint Tuberculosis Committee of the British Thoracic Society. Control and prevention of tuberculosis: a code of practice. *Br Med J* 1983;**287**:1118-21.
20 Department of Health and Social Security. *The social security (industrial injuries) (prescribed diseases) amendment (No 2) regulations 1983*. London: HMSO, 1983. (Statutory Instruments No 1094.)
21 Jachuck SJ, Bound CL. Control and prevention of tuberculosis. *Br Med J* 1983;**287**:1722-3.
22 Caplin M. *The tuberculin test in clinical practice*. London: Baillière Tindall, 1980.
23 Anonymous. Tuberculin testing in hospital staff [Editorial]. *Br Med J* 1977;ii:592.
24 Daniels M, Ridehalgh F, Springett VH, Hall IM. *Tuberculosis in young adults. Report on the Prophit tuberculosis survey 1935-1944*. London: H K Lewis, 1948.
25 Collins CH. Laboratory-acquired tuberculosis. *Tubercle* 1982;**63**:151-5.
26 Baker LC. A coordinated occupational health service in the NHS [Editorial]. *Br Med J* 1983;**286**: 665-6.

Lymphocytes are rhythmic: is this important?

Immunology is now moving into a new era as new techniques make many established measurements easier and as new, often more complex, analyses show that earlier classifications were too simple. For example, new methods have allowed us to classify lymphocyte populations and to describe subsets of these with immunofluorescent flow cytometry.

Thirty years ago endocrinologists moved into their new era with new methods of measuring hormones and of discovering new hormones and prohormones. As their techniques became simpler and better they were able to make repetitive and more precise measurements. One of the discoveries that followed was that the secretion of hormones is episodic and often rhythmic. Some patterns were no surprise; the hormones concerned in the menstrual rhythms would be expected to be secreted on a cyclical basis. When growth hormone was first measured, however, it was some surprise to find that the pituitary discharges this hormone in episodic bursts, very few during the day and most in the period around waking. (Dawn is therefore the time to identify a growth hormone deficiency.)

Serum cortisone measurements in blood were also found to vary throughout the 24 hours, and initial studies based on six to eight points suggested an almost sinusoidal pattern. In fact, the initial descriptions of the adrenal rhythm turned out to be an oversimplification. Very frequent sampling showed that the rhythm results from episodic surges of secretion of variable frequency—with the surges again being most frequent before waking.[1]

At first these new facts caused difficulties for clinicians concerned with endocrinology, but as they became accepted they were slowly incorporated into strategies of investigation and management. Immunologists are now faced with the evidence that there are similar time dependent variations in the immune system and must respond to them.

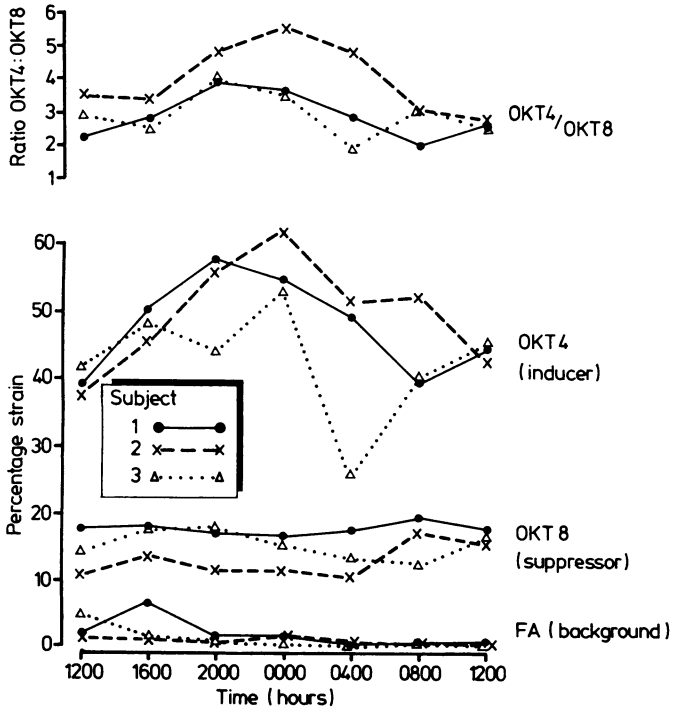
Physicians concerned with immunology must now follow the example of their colleagues in endocrinology and accept as a fact that the immune system is rhythmic. Firstly, we need to decide at what time of day samples used for measurement are to be taken. In some conditions samples may best be taken in the morning, for others in the evening, and in some repetitive sampling may be appropriate. The recognition and definition of any rhythms or episodic variations present should now be considered an essential part of the investigation of any newly identified body constituent, and this approach is essential if the best use is to be made of new methods of assay. Indeed, there may be some circulating materials that come out only at night but are of importance and are still to be discovered because of a failure to consider this possibility.

Studies on circadian changes in T lymphocyte subsets were the main topics of two papers in the *BMJ* and also in other papers published elsewhere during 1983.[2-5] Some of these publications and others on immunology and immune responses are discussed below, already having been reviewed by us in other journals.[6 7 7a] Some disease processes are also episodic, and as the immune or inflammatory responses that are associated with them are rhythmic there may well be a relation.[8 9] The episodic "rhythmic" changes seen in biology that may influence disease range in frequency with evidence of rhythms that are ultradian (shorter than 24 hours), circadian (around 24 hours), and infradian (greater than 24 hours—for example, around seven days (circaseptan), around 28 days and yearly (circannual)).

The study of rhythms in the immune system that may be relevant to the causes of illness, or to the body response to an illness, has been neglected by immunologists and by physicians despite elegant and well documented studies of rhythms in the number of circulating white blood cells and lymphocytes,[10 11] the responses of lymphocytes in vitro,[12-14] and the immune responses to which they contribute.[15 16] There are differences in the anti-inflammatory and immunosuppressant effects of a drug when the same dose is given at different times.[17-19] We have suggested, supported by evidence which is circumstantial rather than conclusive, that events of clinical importance which are episodic in their manifestations may be the result of the immune system (or the associated inflammatory responses) being rhythmic. Two examples are the early morning exacerbations in rheumatoid arthritis,[8] and the tendency for the onset of rejection of a renal allograft to take place at night,[9] and with recurrences around every seven days.[20] The absence of descriptions of repetitive clinical patterns in other clinical settings where the immune system is concerned might simply be due to the appropriate studies not having been done. Negative studies tend to gather dust in an investigator's file, and clinical studies showing the absence of rhythms may exist but have not been published. If

they have been done they should be published; if not then such studies should be initiated.

The new techniques which allow definition of lymphocyte subpopulations allowed us to look for rhythms in these. With the help of the Cancer Research Campaign Laboratories at the University of Nottingham we took multiple samples each day from a few patients (figure).[4] We observed variations



Results of T cell subset measurements obtained from three patients with rheumatoid arthritis at seven different time points in 24 hours.

within the 24 hours and variations in certain lymphocyte subsets in different groups of patients with rheumatoid arthritis studied only at the expected times of "minimum" and "maximum" (table). Recent reports from Australia,[2] Scotland,[3] and France[5] have given similar results in healthy people using a wider range of antisera to identify more lymphocyte subsets. These studies show broad agreement on a range of lymphocyte subpopulations but some observations appear to be in conflict—possibly because the studies were done at different times in the year.[21]

Some of the variations observed in some of the circulating lymphocyte subsets were so large that any normal range for

*Results of T cell subset measurements at 0000 and 0800 hours obtained from healthy controls (C) and patients with rheumatoid arthritis receiving penicillamine (Pn) and gold (Au). Results are mean (SD) values for OKT8+ cells (×10/l) with statistical comparisons between clock times of sampling and subject groupings**

Group	Sample time 0000	Sample time 0800	Significance of time comparisons
Penicillamine (Pn)	0·71 (0·22)	0·51 (0·18)	p<0·01 28%
Gold (Au)	0·50 (0·22)	0·27 (0·08)	p<0·05 46%
Controls (C)	0·67 (0·36)	0·52 (0·33)	NS (p>0·10) 22%
Significance of group comparisons at 0800	Pn *v* Au	p<0·02	
	Au *v* C	p>0·05	
	Pn *v* C	NS (p>0·90)	
		Au = 89% lower than Pn	
		Au = 93% lower than C	

**In samples taken at midnight there were no significant differences between groups, whereas there were significant differences evident between treatment groups in samples obtained at 0800. Although level of OKT8+ positive cells did not change overnight in controls, there were significant differences when samples at two clock times were compared for groups receiving penicillamine or gold.

these should now specify a time for collection (as with the serum cortisol measurements used in endocrinology) if the normal range is to be meaningful. The implications of rhythmic fluctuations may be much wider than just this need to standardise sampling times. Our own observations in patients with rheumatoid arthritis make a very small start to a very large undertaking—and one which will be expensive in terms of resources and time. Some illnesses may, however, be understood only if they are studied in this dynamic way in relation to time, considering immunology as a "moving picture" rather than with only static "snapshot" observation.

Rhythmic variation in the function of tissues and organs is also of importance in the context of the administration of drugs and hormones. When the glucocorticoid hormones first became reasonably easy to measure (in the early 1960s) the time of their administration was found to have a critical effect on their effect on the body, in particular in relation to interference with the adrenopituitary feedback mechanisms of endogenous production of cortisol.[1] Diagnostic tests using a nocturnal dose of dexamethasone were developed to investigate patients with suspected Cushing's syndrome, and are now also being used by some in the diagnosis of psychiatric disorders, in particular depression.[22,23] Experimental and clinical observations have made it quite certain that the time of administration of glucocorticoids may have an important effect on other aspects of their activity, and this may be relevant both to their effectiveness and to their toxicity.[7,7a,17,24]

Single morning doses of prednisolone are still not yet standard practice, even in those circumstances where this approach is both logical and has been shown to work. In many other settings in which corticosteroids are an established method of treatment we still do not know the correct time for administration. We have even less information on most of the other drugs used to interfere with the immune process or with inflammation. Nevertheless, cyclosporin A may be more effective at prolonging allografts at some times than at others[25]; in the future we might hope that studies of the optimum time for administration of any new immunosuppressant might precede its introduction to clinical use. The possibility that time is important has not been a topic of sufficient interest to most immunologists, pharmacologists, or even to the clinicians who advise patients. When asked by a patient "when do I take the treatment?" most physicians do not know the answer, even when a once a day regimen is proposed.

In a review article entitled "Immunology has rhythm," written in 1980, we asked a series of questions to the reader of a then new publication that provides news and reviews for immunologists.[6] Our answers to those questions have not changed since 1980, but now there are more facts to support the opinions given in those answers. We answered "yes" to four questions—"Can techniques used in the study of biological rhythmicity assist the search for basic information about immune responses?" "Can immune responsiveness become apparent tolerance simply by altering the time of exposure to an antigen?" "Are physiological and immunological responses different at different times?" and "Can single time point studies be misleading?" We also asked "May circadian rhythms in immune responses be important to the clinician?" and answered "potentially." It is a reflection of current clinical research and its funding that it has taken so long for a potential to become a certainty. We had, and still have, no doubts that immune responses have rhythms.[6,7,7a,26] More facts are needed, however, and the implications of those known need more discussion. A recent review article on the topic of the well documented circadian

variations in airways resistance did not mention much of the carefully documented early studies of this phenomena and of its interrelations with histamine responses and with circadian variations in direct hypersensitivity responses.[26 27] Many other authors have also failed to explore the rather elusive publications on chronobiology published over the past two decades.

Those who have not taken an interest in the relevance of rhythmicity to their clinical or biological interests may find useful the reviews from those groups who have. The reports of some of the symposia they attended provide a route to many of the earlier publications.[6 7 7a 14 24 26 28-33] In the future these may be seen to have an importance not perceived at the time. A leading article in the *BMJ* in 1979 could refer to only a handful of reports correlating immunity and biological rhythmicity; now a library search would yield more than 400.[33]

MARTIN S KNAPP
Senior research fellow

ROY POWNALL
Senior scientist

Unit of Medical Information Technology,
Department of Obstetrics and Gynaecology,
University Hospital,
Nottingham NG7 2UH

1 Kreiger DT. Rhythms in CRF, ACTH and corticosteroids. In: Kreiger DT, ed. *Endocrine rhythms*. New York: Raven Press, 1979:123-42.
2 Bertouch JV, Roberts-Thomson PJ, Bradley J. Diurnal variation of lymphocyte subsets identified by monoclonal antibodies. *Br Med J* 1983;**286**:1171-2.
3 Ritchie AWS, Oswald I, Micklem HS, *et al*. Circadian variation of lymphocyte subpopulations: a study with monoclonal antibodies. *Br Med J* 1983;**286**:1773-5.
4 Pownall R, Ward C, Knapp MS. Circadian variation of helper and suppressor T cells and disease activity in rheumatoid arthritis. *Chronobiologia* 1983;**10**:148.
5 Levi F, Cannon C, Blum JP, Reinberg A, Mathe G. Large amplitude circadian rhythm in helper: suppressor ratio of peripheral blood lymphocytes. *Lancet* 1983;ii:462-3.
6 Pownall R, Knapp MS. Immune responses have rhythms: are they important? *Immunology Today* 1980;**1**:7-10.
7 Knapp MS. Chronobiology: a subject of importance to the rheumatologist? *Br J Clin Pract* 1984;**38**(symp suppl 33):1-7.
7a Pownall R. Biological rhythms in cell-mediated immunity: their relevance in rheumatology. *Br J Clin Pract* 1984;**38**(symp suppl 33):20-3.
8 Kowanko IC, Pownall R, Knapp MS, Swannell AJ, Mahoney PGC. Circadian variations in the signs and symptoms of rheumatoid arthritis and in the therapeutic effectiveness of flurbiprofen at different times of day. *Br J Clin Pharmacol* 1981;**11**:477-84.
9 Knapp MS, Cove-Smith JR, Dugdale R, Mackenzie N, Pownall R. Possible effect of time on renal allograft rejection. *Br Med J* 1979;i:75-7.
10 Abo T, Kawate T, Itoh K, Kumagai K. Studies on the bioperiodicity of the immune response I. Circadian rhythms of human T, B and K cell traffic in the peripheral blood. *J Immunol* 1981;**126**:1360-3.
11 Shaw AFB. The diurnal tides of the leucocytes of man. *Journal of Pathology and Bacteriology* 1927;**30**:1-19.
12 Eskola J, Frey H, Molnar G, Soppi E. Biological rhythm of cell-mediated immunity in man. *Clin Exp Immunol* 1976;**26**:253-7.
13 Tavadia HB, Fleming KA, Hume PD, Simpson HW. Circadian rhythmicity of human plasma cortisol and PHA—induced lymphocyte transformation. *Clin Exp Immunol* 1975;**22**:190-3.
14 Haus E, Lakatua DJ, Swoyer J, Sackett-Lundeen L. Chronobiology in hematology and immunology. *Am J Anat* 1983;**168**:467-517.
15 Pownall R, Knapp MS. Circadian rhythmicity of delayed hypersensitivity to oxazalone in the rat. *Clinical Science and Molecular Medicine* 1978;**54**:447-9.
16 Cove-Smith JR, Kabler P, Pownall R, Knapp MS. Circadian variation in an immune response in man. *Br Med J* 1978;ii:253-4.
17 Knapp MS, Pownall R. Circadian rhythm in immune responses and in the effects of glucocorticoids. *Allergologie* 1980;**3**:5226-30.
18 Pownall R. Knapp MS. A circadian study of corticosteroid suppression of delayed hypersensitivity. *Int J Immunopharmacol* 1980;**1**:293-8.
19 Labrecque G, Dore F, Laperriere A, Perusse F, Belanger PM. Chronopharmacology II—variations in the carrageenin-induced oedema, in the action of the plasma levels of indomethacin. In: Reinberg A, Halberg F, eds. *Chronopharmacology*. Oxford: Pergamon Press, 1979:231-8.
20 de Vecchi A, Cantaluppi A, Ponticelli C, Halberg F, Southern RB. Circaseptan rhythmic aspects of rejection in treated patients with kidney transplants. In: Walker C, Winget CM, Soliman KFA, eds. *Chronopharmacology and chronotherapeutics*. Florida: A and M University Foundation, 1981:339-54.
21 Levi FA, Canon CH, Blum JP, *et al*. Circadian rhythms in circulating lymphocyte subsets in healthy men: a 100-fold variation may be physiologic. In: Reinberg A, Smolensky M, Labreque G, eds. *1st Montreux international symposium on biological rhythms and medications*. Oxford: Pergamon Press (in press).
22 Knapp MS, Keane PM, Wright JG. Circadian rhythm of plasma 11-hydroxycorticosteroids in depressive illness, congestive heart failure, and Cushing's syndrome. *Br Med J* 1967;ii:27-30.
23 Anonymous. The new psychiatry [Editorial]. *Br Med J* 1981;**283**:513-4.
24 Kowanko IC, Pownall R, Knapp MS, Swannell AJ, Mahoney PGC. Time of day of prednisolone administration in rheumatoid arthritis. *Ann Rheum Dis* 1982;**41**:447-52.
25 Liu T, Cavallim M, Halberg F, *et al*. Toward a circaseptan and circadian cyclosporine chronotherapy of rats with segmental pancreatic allografts. In: Reinberg A, Smolensky M, Labreque G, eds. *1st Montreux international symposium on biological rhythms and medications*. Oxford: Pergamon Press (in press).
26 Reinberg A, Smolensky MH. *Biological rhythms and medicine*. Berlin: Springer-Verlag, 1983.
27 Barnes PJ. Nocturnal asthma: mechanisms and treatment. *Br Med J* 1983;**288**:1397-8.
28 Scheving LE, Halberg F, Pauly JE, eds. *Chronobiology*. Tokyo: Igaku Shoin, 1974.
29 Walker CA, Winget CM, Soliman KFA, eds. *Chronopharmacology and chronotherapeutics*. Florida: A and M University Foundation, 1981:1-411.
30 Scheving LE, Mayersbach HV, Pauley JE. An overview of chronopharmacology. *J Europ Toxicol* 1974;7:203-7.
31 More-Ede MC, Sulzman FM, Fuller CA. *The clocks that time us*. Cambridge, USA: University of Harvard Press, 1982.
32 Minors JM, Waterhouse DS. *Circadian rhythm and the human*. Bristol: Wright, 1981.
33 Anonymous. Chronotherapeutics, a new clinical science [Editorial]. *Br Med J* 1978;i:1376.

Drug interactions and β blockers

β adrenoceptor antagonists interact with many drugs with which they may be given simultaneously, but neither the frequency nor the clinical importance of most of these interactions has been clearly established. An interaction may change the response to either the β blocker or the other drug or potentiate an unwanted effect that they share. The mechanism may be either pharmacokinetic or pharmacodynamic.

Pharmacokinetic interactions result from changes in hepatic oxidative drug metabolism.[1] They occur mainly with the more lipid soluble β blockers such as propranolol and metoprolol, which are extensively metabolised and have a high first pass clearance[1]; to a less extent with acebutolol and oxprenolol; and not at all with atenolol, sotalol, nadolol, and pindolol, which are eliminated unchanged by the kidney. Enzyme inducing drugs increase the clearance of metabolised β blockers and reduce the bioavailability of those with a high first pass metabolism.[2] Thus cimetidine increases the bioavailability of propranolol and metoprolol.[3 4] The clearance of extensively metabolised β blockers is also influenced by hepatic blood flow. This is the mechanism by which hydralazine reduces the first pass clearance of propranolol and metoprolol, increasing the plasma concentrations when these drugs are given by mouth.[5 6] The changes in the blood concentration of β blockers that result are, however, usually small and clinically unimportant.

β blockers can themselves reduce the clearance of other drugs, both by inhibiting hepatic oxidative metabolism and by reducing hepatic blood flow secondary to the fall in cardiac output which they produce.[1] Inhibition of drug metabolism occurs mainly with the extensively metabolised lipid soluble β blockers, propranolol and metoprolol, and the fall in hepatic blood flow is greatest with β blockers without intrinsic sympathomimetic activity. Propranolol and metoprolol reduce the clearance of lignocaine by both mechanisms[7 8] and may produce lignocaine toxicity.[9] Propranolol increases the blood concentrations of chlorpromazine by inhibiting its metabolism, an interaction which may explain earlier reports of a beneficial effect of propranolol in schizophrenic patients receiving chlorpromazine.[10] Propranolol[11 12] and possibly metoprolol, but not atenolol,[13] inhibit the metabolism of coumarin anticoagulants. The effect on prothrombin time proved to be small in healthy volunteers, but it might be important in fully anticoagulated patients.

Pharmacodynamic interactions with β blockers are usually more important than the pharmacokinetic interactions, and most can be predicted from the known pharmacological effects of the interacting drugs. Thus β blockers potentiate the unwanted effects of many antiarrhythmic drugs, increasing the risk of myocardial depression, cardiac failure, hypotension, bradycardia, atrioventricular block, and asystole. Clinically important interactions have been reported with verapamil,[14] disopyramide,[15] lignocaine,[9] and tocainide,[16] and potentiation of the negative inotropic effect of other class I antiarrhythmic agents should be expected. In patients whose cardiac function is already impaired the combination of nifedipine and a β blocker can produce severe hypotension and heart failure.[17]

Sotalol differs from other β blockers in having class III antiarrhythmic activity at therapeutic doses. Thus it prolongs the Q-T interval and may increase the risk of ventricular arrhythmias. This risk appears to be greater in patients with hypokalaemia induced by diuretics[18] and sotalol is perhaps not a suitable β blocker for use with a thiazide diuretic.

The antihypertensive effect of β blockers is antagonised by