resulted also in a marked decrease in the incidence of "new thrombosis" diagnosed from the third day onwards: two legs thrombosed in the treated group but 10 in the untreated group. How can such brief treatment have a continuing protective effect between the third and the sixth days?

May I suggest that the thrombi diagnosed for the first time after the second day may in fact have existed since the operation but were too small originally to be detected with certainty by this method and that intermittent compression usually prevented the formation of these tiny thrombi also. I suspect that "thrombi" varying in size from a few platelet aggregates up to 1 cm in length[1] are often formed, especially when conditions are favourable as during an operation. They are clinically silent and usually disappear without trace. These then represent a potentially dangerous nidus on which clinically evident thrombi can grow, again given appropriate conditions.

This raises the problem of whether to attempt to treat ever-smaller subclinical thrombi or to aim at preventing their growth.

It is also of interest that Dr. Roberts and Mr. Cotton think that thrombosis in malignancy may constitute a special case. We have studied 41 surgical patients before (as well as after) operation, and followed them up to see if they developed thrombosis. The patients preoperatively differed from controls in many platelet function tests and the presence of malignancy accounted for most but not all of these differences.[2]—I am, etc.,

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1 Havig, Ø., International Congress of Thrombosis and Haemostasis Abstract IV, Paper 239, Vienna 1973.
2 O'Brien, J. R., Tulevski, V. G., Etherington, M., Madgwick, T., Alkjaersig, N., and Fletcher, A., *Journal of Laboratory and Clinical Medicine*, 1974, **83**, 342.

Chronic Brucellosis

SIR,—Many will conclude from the letter from Sir James Howie (16 March, p. 516) that the antibiotic of choice in the treatment of chronic brucellosis is clomocycline. I have not used this preparation but there would seem little reason, on theoretical grounds and from a search of the literature, to prefer it to tetracycline 2 g daily, combined at first with intramuscular streptomycin. Could Sir James kindly say whether in his patient this regimen had been tried and had failed, and whether he considers that the duration of follow-up after treatment with clomocycline alone was long enough to ensure against the possibility of relapse?

Clomocycline has been claimed to be effective in avoiding the colonic disturbances associated with prolonged antibiotic therapy[1] but in my experience it is rarely necessary to discontinue tetracycline for this reason. To an impoverished exchequer, incidentally, the cost of treating with clomocycline for six weeks is £13·18 or more and with tetracycline for the same period £4·09 or less—in hospital very much less.—I am, etc.,

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1 Payne, D., *Medicine (London)*. 1972, pt. 6, 499.

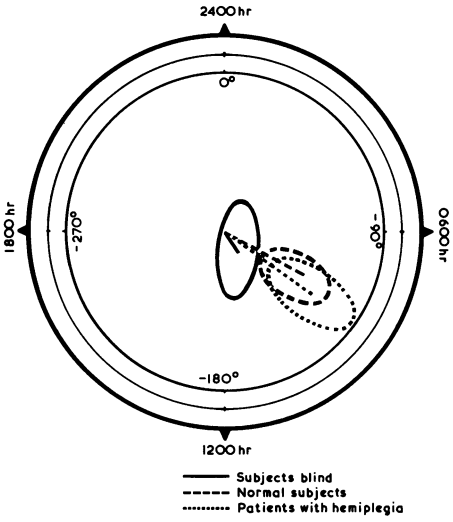
Circadian Rhythm of Cortisol Secretion in Elderly and Blind Subjects

SIR,—At the recent conference of the World Medical Association (3 November, p. 292), some applications of computers in medicine were discussed, such as automation of medical laboratories, rationalization of medical reporting, and analysis of biosignals.

Halberg *et al.*[1 2] developed a technique to study biorhythm by computer (microscopic evaluation of data or Cosinor). We have used this technique to evaluate the data collected in an investigation of the circadian rhythm of human plasma cortisol concentrations in elderly normal subjects, in elderly patients with cerebrovascular hemiplegia, and in blind subjects.[3 4]

Forty elderly male volunteers, grouped as follows, were observed: (1) 18 normal subjects aged 62-88 (average 73·11 years; (2) 11 patients with cerebrovascular hemiplegia aged 62-83 (average 67·09) years; and (3) 11 patients with total chronic blindness for 4-12 years but with otherwise intact nervous system, aged 65-93 (average 74·27) years. All the patients had been in hospital for six months and had a 5-7 hour sleep rhythm (from 10 or 11 p.m. to 5 or 6 a.m.). Blood samples were drawn every three hours, starting at 6 a.m., for 24 hours or in some cases for 48 hours. The plasma cortisol was analysed by Mattingly's fluorimetric method. The data obtained were analysed by the Cosinor method in the chronobiology laboratory of the University of Minnesota by courtesy of Professor F. Halberg.

The accompanying figure shows that in the normal subjects and in the patients with hemiplegia the error ellipse does not overlap the origin of the circle, which is significant evidence of a rhythm ($P = 0·001$). In the blind subjects the error ellipse covers the origin of the circle, so that there is no statistically significant evidence of rhythmical variations ($P = 0·150$). There are three possible interpretations of this last finding:



(1) loss of synchonizer light stimuli in blind people, particularly of the light/darkness alternating stimulus; (2) free-running rhythms[5] in blind people, with periods other than 24 hours and desynchronized in each subject; or (3) circannual desynchronization in blind people whereby the different phase of circannual rhythm might overly the circadian rhythm variations.

Answers to these questions may be eventually provided by prolonged longitudinal studies and by repeated studies performed at yearly intervals in order to detect free rhythms and/or circannual variations. It seems certain, however, that lack of the light synchronizer modifies in some way the plasma cortisol biorhythm.—We are, etc.,

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1 Halberg, F., Engeli, M., Hamburger, C., and Hillman, D., *Acta Endocrinologica*, 1965, Suppl. 103, p. 54.
2 Halberg. F., Tong, Y. L., Johnson, A., in *The Cellular Aspects of Biorhythms*, ed. H. von Mayersbach. Berlin, Springer, 1967.
3 Bellastella, A., Colucci, C. F., D'Alessandro, B., *Riforma Medica*, 1972, **86**, 18.
4 Bellastella, A., Colucci, C. F., D'Alessandro, B., *Bollettino della Societa Italiana di Biologia Sperimentale*, 1972, **48**, 592.
5 Orth, D. N., Island, D. P., *Journal of Clinical Endocrinology and Metabolism*, 1969, **29**, 479.

Reactions to Immunization

SIR,—We wish to comment on some of the points raised in a recent edition of the "Nationwide" television programme, when Mr. Jack Ashley, M.P., and Professor George Dick discussed immunization. With particular reference to Professor Dick's statement that it is "important that babies are immunized by general practitioners because they are the people who know all about the babies and the families, whereas the clinic doctors may only see the baby for one time—that is, when he is being immunized," we would point out that immunization clinics are carried out in many child health centres all over the country by departmental medical officers, who until 31 March 1974 have constituted the medical staff of the local health authorities.

These doctors follow up the babies routinely at regular intervals for full developmental and physical examinations, apart from the examinations they carry out in conjunction with the immunization. They also ensure that they are acquainted with all the intercurrent illnesses and are helped to acquire this information by their close and constant association with health visitors. Full reports of such illnesses are routinely requested from general practitioners or hospital physicians.

Many of these doctors have a postgraduate qualification. Immunization is an important part of their work in the preventive sphere and all have to ensure that their knowledge of the hazards of immunization procedures remains up to date. On the whole they have more time than the general practitioner to discuss medical problems and explain reactions to parents. Some general practitioners, anyway, prefer not to do this work because they would be unable, for time reasons, to maintain a high level of immunization. Dr. E. P. James's letter (16 February, p. 287) does bring up exactly the