prevalence of transient and stable complete heart block is therefore likely to be more accurate than the estimates of previous workers who derived their data from hospital or cardiac department attendance records.

The patients with heart block seen in this survey tended to have had less severe symptoms or signs of circulatory disturbance than had those recorded in previous reports (Table VIII). Syncopal attacks occurred in less than half of the

TABLE VIII.—Comparison of Frequency of Syncopal Attacks and Cardiac Failure in Patients with Heart Block found in this Survey with that Reported by other Authors

Author	Syncopal Attacks	Congestive Cardiac Failure	No. of Patients
	%	%	
Zoob and Shirley Smith (1963)	77	—	30
Hanssen (1949)	63	44	66
Johansson (1966)	63	22*	116†
Penton <i>et al.</i> (1956)	61	40	224
Devon Heart Block Survey	48	9	100

*Assessed on 55 survivors only.

†Total excluding those with myocardial infarction and Digitalis intoxication.

patients in Devon (48%), whereas Siddons and Sowton (1967) considered 67% to be the usual frequency, and the authors quoted in Table VI give similar figures, all being within the range of 61-77%. The difference in frequency of cardiac failure tended to be even greater in that only 9 of the 100 survey patients had evidence of this compared with a frequency of 20-44% found by previous authors (Hanssen, 1949; Penton *et al.*, 1956; Zoob and Shirley Smith, 1963; Johansson, 1966).

It is possible that the differences between the patients of this survey and those of other series are fortuitous, but it is at least as probable that they reflect a true difference between the clinical condition of heart block as it occurs in the population as a whole and that seen in the specially selected group of patients who attend hospital.

The report of the Cardiology Committee of the Royal Col-

lege of Physicians (1967) suggested that pacemakers should be fitted in about half of the patients with complete heart block. Current experience in the cardiac department in Exeter has been in line with this report and about 40% of patients with block referred within the past five years now have permanent pacemakers. In contrast, only 12 of the 100 patients in the present survey had pacemakers. The few fitted would seem to reflect the rather more benign nature of the condition of heart block seen in the survey patients rather than conservatism on the part of their medical advisers, since only 13 not fitted with pacemakers were found to be still suffering from Adams-Stokes attacks. If the figures for morbidity in heart block presented here are representative for the general population they lend support to the present policy of recommending pacemakers in selected patients only, rather than making pacemaking obligatory once heart block has been diagnosed.

We would like to thank the South Western Faculty of the Royal College of General Practitioners and the family doctors in the Exeter clinical area for their help and co-operation, on which this study depended. We are grateful for the support of the other physicians in the Devon clinical area who referred patients and also kindly allowed us to borrow case-notes. We acknowledge the help and advice of Mr. Dennis Gillings and Dr. N. G. Pearson, of the Institute of Biometry and Community Medicine, University of Exeter, in obtaining population data and in interpreting the results. Part of this work was financed by a grant from the Department of Health and Social Security.

REFERENCES

- Ashford, J. R., and Pearson, N. G. (1968). In *Computers in the Service of Medicine*, edited by G. MacLachlan and R. A. Shegog, vol. 1, p. 175. London, Oxford University Press.
- Cardiology Committee of the Royal College of Physicians (1967). Report on Pacemakers for the Treatment of Heart Block. London.
- Hanssen, P. (1949). *Acta Medica Scandinavica*, 136, 112.
- Johansson, B. W. (1966). *Acta Medica Scandinavica*, Suppl. No. 451.
- Penton, G. B., Miller, H., and Levine, S. A. (1956). *Circulation*, 13, 801.
- Siddons, H., and Sowton, E. (1967). *Cardiac Pacemakers*. Springfield, Thomas.
- Stock, J. P. P. (1969). *Diagnosis and Treatment of Cardiac Arrhythmias*. London, Butterworths.
- Zoob, M., and Smith, S. K. (1963). *British Medical Journal*, 2, 1149.

Supervision of Epileptic Patients Taking Phenytoin

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British Medical Journal, 1970, 1, 147-149

Summary: Serum phenytoin concentrations in outpatients and inpatients with epilepsy have been contrasted. Individual patients were receiving prescriptions ranging from 100 to 300 mg. of sodium phenytoin daily, but the two groups were comparable in respect of dosage, age, and sex distribution. Whereas the mean phenytoin concentration among 14 inpatients was 28 µg./ml. that among 15 outpatients was only 15.7 µg./ml. When the supervision of a further 12 outpatients was changed to include more frequent visits and regular provision of blood samples their mean serum concentration of phenytoin rose from 17.5 to 27.7 µg./ml.

The results indicate that failure to follow dosage instructions is a factor of major importance among epileptic patients whose response to treatment is inadequate or erratic.

Introduction

Patients with epilepsy may be free of symptoms for long periods; their treatment is always prolonged and its success sometimes uncertain, and unwanted effects are common. It would not be surprising if some patients took their drugs erratically, and reports from Scandinavia and North America suggest that a high proportion of epileptic patients take fewer tablets than those prescribed. Buchthal, Svensmark, and

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	No. and sex	Mean Age Years $\pm$ S.D.	No. taking Phenobarbitone	Mean dose Phenytoin (mg./day)	Mean serum Phenytoin ($\mu\text{g./ml.} \pm$ S.D.)
Initial study:					
Outpatients	15 (7M., 8F.)	43 $\pm$ 27	5	225	15.7 $\pm$ 12.9
Inpatients	14 (6M., 8F.)	46 $\pm$ 18	7	200	28.0 $\pm$ 8.1
Prospective study	12 (3M., 9F.)	41 $\pm$ 19	10	200	{ Initial: 17.5 $\pm$ 14.7 Final: 27.7 $\pm$ 7.3

Schiller (1960) found that 24 out of 51 outpatients receiving phenytoin had a serum concentration of less than 10 $\mu\text{g./ml.}$ They inferred, without other evidence, that this was a result of irregular dosage. Kutt, Haynes, and McDowell (1966) noted that of 16 patients with uncontrolled seizures admitted to hospital for investigation of low serum phenytoin concentrations a pronounced rise occurred in 12 with no change in the prescribed dose. Lund, Jørgensen, and Kühl (1964) measured the serum phenytoin concentrations of 51 outpatients. Twenty-two were seen two and six weeks later, and those with low serum values were told that their co-operation was suspect. After 12 weeks 17 of the 22 had a serum phenytoin concentration greater than 10 $\mu\text{g./ml.}$ In contrast only 10 of the remaining 29 patients, who were not seen meanwhile, attained this concentration. The difference was highly significant ($P < 0.005$).

This study has confirmed the serious extent of the problem and shows that, without using embarrassing confrontations that might produce alienation and defaulting, changes in routine supervision can stimulate most patients to take phenytoin more reliably.

Methods

Patients of both sexes were included in the study. All were over 15 years of age and had either idiopathic or symptomatic epilepsy, the latter for a period of at least 10 years. All had received anticonvulsants, including phenytoin, from a general neurological clinic or a medical clinic for at least six months previously. None was in an epileptic colony and none had received psychiatric treatment in the previous year. No other criterion of selection or rejection was used; all suitable patients were accepted into the study as they presented in the clinic.

Two comparisons were made. Serum phenytoin concentrations were contrasted in outpatients and inpatients on similar treatments. A further series of outpatients were then studied prospectively over a period of eight months. During this time several changes were made in their routine management. A special seizure clinic was organized. Patients were seen, when possible, every eighth week; previously they had attended at intervals of up to six months. They were given a reserve of tablets to reduce the risk of exhausting their supply and were asked to return any remaining at their next attendance. They were urged to record their seizures on diary cards. Blood samples for phenytoin estimations were taken during the early afternoon at each attendance. Patients were told only that the results of blood tests were used to assess their progress. The clinicians did not see these results until the end of the study. The serum phenytoin values for each patient at the beginning and towards the end of the period were contrasted.

Phenytoin was extracted from the serum samples, separated from phenobarbitone when necessary, and measured spectrophotometrically by the methods of Svensmark and Kristensen (1963). The spectrophotometer readings were made relative to a series of standard solutions.

Results

Serum Phenytoin Estimations.—Duplicate extractions of the phenytoin content of the sera under blind conditions produced

results consistent within $\pm 2.44 \mu\text{g./ml.}$ (S.D.). Those samples passing through the phenobarbitone extraction procedure did not provide results that differed systematically from the remainder.

Clinical Studies.—Details of the patients and the mean serum concentrations of phenytoin within the various groups are shown in the Table. All inpatients had been in hospital for at least five days before they provided blood samples.

The serum concentration of phenytoin was not related to prescribed dose within any group, but the mean value among the inpatients (28.0 $\mu\text{g./ml.}$, S.D. ± 8.1) was almost twice as high as that of the outpatients seen under routine conditions (15.7 $\mu\text{g./ml.}$, S.D. ± 12.9). Though this difference is highly significant ($t = 4.0$, D.F. = 27, $P < 0.01$) on parametric testing, the validity of the test is questionable because the preponderance of anomalous low values within the outpatient group increased the variance of the results and produced a serious departure from normality. A non-parametric test, however, confirms the significance of the contrast: 9 out of 15 outpatients but only 1 out of 14 inpatients had a serum concentration below the therapeutic threshold of 15 $\mu\text{g./ml.}$ (quoted by Buchthal *et al.* (1960); $P = 0.03$, Fisher's test two-tailed).

The mean initial concentration of phenytoin with the group of outpatients studied prospectively (17.5 $\mu\text{g./ml.}$, S.D. ± 14.7) was similar to that of the first group of outpatients studied, but after the patients had undergone 26 to 30 weeks of more intensive supervision the mean serum concentration rose to 27.7 $\mu\text{g./ml.}$ (S.D. ± 7.3) and approached that of the inpatients. Initially 6 of the 12 outpatients had a serum concentration below 15 $\mu\text{g./ml.}$; at the close only one patient had a value in this range. The initial results from the outpatients again depart from normality, but the changes within individuals over the period of study are not significantly skewed:

Initial serum phenytoin measurements and subsequent increments within the group of outpatients. Increments after 26 to 30 weeks of modified supervision.

$g = 0.35$; $t = 0.56$; $P > 0.5$, where g is a measure of skewness (Snedecor, 1956), and the mean change (10.2 $\mu\text{g./ml.}$, S.E. ± 4.4) is significantly different from zero ($P < 0.01$). Patients with low initial serum concentrations tended to produce the largest increments (see Chart). The regression coefficient of increments

on initial concentrations ($b = -0.87$) is highly significant ($t = 3.2$; D.F. = 2; $P < 0.01$).

Of the 12 patients studied prospectively six had initial serum phenytoin concentrations below 15 $\mu\text{g./ml.}$; none of these had symptoms or signs suggestive of phenytoin toxicity. All but one of the remainder had some gum hypertrophy and this was of moderate degree in the patient with the highest initial value, 51 $\mu\text{g./ml.}$ Nystagmus was induced in one patient who had a serum concentration of 40 $\mu\text{g./ml.}$ Three others were reported to show slight apathy.

Reduction in frequency of fits was not related to the increase in the mean phenytoin concentration within this group, but the relatively short period of study reduced the sensitivity of the test.

Discussion

Wide and unpredictable variation in the serum concentrations of phenytoin at first cast doubt on our methods of extraction and estimation of the drug. There was, however, no apparent source of important error; duplicate measurements under blind conditions gave reproducible results, standards in a variety of sera gave consistent readings, the absorption spectra of standards and samples were similar, and no extract from the pooled sera used for blank estimations produced an absorption band with a peak at 235 $m\mu$.

Confidence in our techniques was restored when a consistent pattern emerged between the results of the four groups of patients examined. The initial concentration of phenytoin among those studied prospectively was similar to that of the other outpatients: 17.5 and 15.7 $\mu\text{g./ml.}$ respectively (see Table). In contrast, at the end of the period of modified supervision the mean concentration among the outpatients had risen to approach that of the inpatients: 27.7 and 28.0 $\mu\text{g./ml.}$ respectively. The tendency for those patients with low initial phenytoin concentrations to show large increments during the study supports the interpretation that they were encouraged to take their drugs as prescribed. Moreover, the mean concentration attained suggests that a high degree of co-operation was achieved within the group and that the remaining disparity in serum concentrations between patients is due largely to factors other than dosage. Two inpatients and two outpatients taking only 100 mg. of phenytoin daily provided

samples containing more than 30 $\mu\text{g./ml.}$ None of the patients on the prescribed doses of 200 or 300 mg. per day attained higher concentrations, but in no instance did the concentration remain below 10 $\mu\text{g./ml.}$ It is likely that for most patients a serum concentration of 10 to 20 $\mu\text{g.}$ of phenytoin per ml. has a therapeutic effect (Buchthal *et al.*, 1960; Kutt and McDowell, 1968). Some patients can maintain this concentration on a dose of 100 mg./day, others either absorb the drug less efficiently or eliminate it more rapidly (Kutt *et al.*, 1966). None the less, failure to take treatment as prescribed is evidently an important cause of low serum concentrations in many instances.

Since in this study several modifications of outpatient supervision were introduced simultaneously, the contribution of each to improved co-operation cannot be determined. Establishment of a separate seizure clinic, more frequent appointments, provision of diary cards for recording fits, and requests for blood samples all demonstrated to the patients the increased attention given to their problem. Tablets were supplied in excess of immediate needs, so a reserve was available if the appointment was postponed. Morale appeared to improve, and premature confrontations with the patients were avoided by withholding the phenytoin values from the clinicians until the end of the study.

Little is known about the optimum use of anticonvulsant drugs because the difficulties of performing adequate controlled assessments are formidable. Clearly, no simple relation holds between prescribed dosage and serum concentration, and whenever clinical progress is unsatisfactory treatment should be modified in the light of the serum concentration rather than the oral dosage. Unreliable patients and others with a persistently low serum concentration will be detected and toxic responses resulting from inadvertent overdose should be reduced.

REFERENCES

- Buchthal, F., Svensmark, O., and Schiller, P. J. (1960). *Archives of Neurology*, **2**, 624.
- Kutt, H., Haynes, J., and McDowell, F. (1966). *Archives of Neurology*, **14**, 489.
- Kutt, H., and McDowell, F. (1968). *Journal of the American Medical Association*, **203**, 969.
- Lund, M., Jørgensen, R. S., and Kühl, V. (1964). *Epilepsia*, **5**, 51.
- Snedecor, G. W. (1956). *Statistical Methods*, 5th ed., p. 199. Ames, Iowa State University Press.
- Svensmark, O., and Kristensen, P. (1963). *Journal of Laboratory and Clinical Medicine*, **61**, 501.

Effects of Obesity, Glucocorticoid, and Oral Contraceptive Therapy on Plasma Glucose and Blood Pyruvate Levels

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British Medical Journal, 1970, **1**, 149–152

Summary: The plasma glucose and blood pyruvate levels were determined after oral glucose tolerance test in six groups of women: non-obese and obese controls and in non-obese and obese women receiving glucocorticoid or oral contraceptive therapy. The mean fasting plasma glucose level was similar in all groups, but glucose tolerance was impaired in the obese controls, non-obese women on oral contraceptives or being treated with glucocorticoids, and appreciably impaired in the obese oral contraceptive and glucocorticoid groups compared with mean levels in non-obese subjects of the same groups. Obesity was associated with abnormally raised blood pyruvate levels in response to a glucose tolerance test in all

groups. Striking similarities were observed between the responses of the plasma glucose and blood pyruvate levels to glucose tolerance tests in the obese control and non-obese oral contraceptive and non-obese glucocorticoid-treated groups. It is suggested that these abnormalities result from a common mechanism—namely, glucocorticoid excess.

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