Screening for Breast Cancer

SIR,—The report by Dr. Isobel G. Furnival and others, "Accuracy of Screening Methods for the Diagnosis of Breast Disease," published in your issue of 21 November (p. 461) rightfully brings to the attention of the profession that no single type of examination should be relied upon as a screening method for the detection of early breast cancer. The sensitivity and specificity of such diagnostic measures as physical examination, mammography, and thermography were recently appraised in 862 patients with breast cancer in six large American medical centres on the East coast. This was a conjoint effort under the auspices of the American Cancer Society, and the results were analysed by expert statisticians. All three disciplines were found to have approximately the same degree of diagnostic accuracy: in the neighbourhood of 70%. The combination of all three methods, however, raises the diagnostic accuracy above 90%. It seems obvious to us that the latter is the only tenable approach. In one of our recent reports we furthermore brought attention to the fact that in exceptional instances one or another of these methods of examination will reveal pathognomonic evidence not otherwise appreciated.

In America 95% of women operated on for breast cancer have themselves been responsible for the initial discovery of the lesion. We have long urged that responsibility for the detection of cancer should be taken out of the hands of women and returned to the physician. Periodic examinations of all women over 35 years of age by all modalities available is the only avenue by which we can expect to make a satisfactory impact on the mortality statistics for cancer of the breast.—I am, etc.,

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Interaction between Phenytoin and the Benzodiazepines

SIR,—Rare instances of intoxication in patients taking chlorthalidone and phenytoin have been reported.¹ However, serial

measurements of plasma phenytoin concentration have not been published for patients on this particular combination of drugs.

Over the past two years we have treated patients with phenytoin to evaluate its long-term effect on the reduction of cardiac arrhythmias after myocardial infarction. During this time we noticed an increased incidence of neurological signs of phenytoin toxicity among patients receiving, in addition to phenytoin, chlorthalidone or diazepam. We therefore compared serial plasma estimations of phenytoin in patients taking the drug without additional chlorthalidone or diazepam and patients taking phenytoin together with an additional benzodiazepine drug.

The 124 patients included in this study had been taking either 300 mg or 400 mg of phenytoin daily following discharge from hospital after an acute myocardial infarction. Their plasma levels of phenytoin were measured at six-weekly intervals using a modification² of Wallace's³ method, which is specific for phenytoin. Details of all other therapy were also recorded at six-weekly intervals.

Only five of the 124 patients whose plasma levels of phenytoin were measured had been stabilized on a constant dose of phenytoin before and after the addition of diazepam or chlorthalidone. Weighted means (Table I) were obtained by averaging all six-weekly measurements for each patient on each drug regimen. The number of measurements varied from two to eight for each patient. The mean plasma level of phenytoin was higher in every patient after the addition of a benzodiazepine drug (Table I), but for this small number of patients the difference in plasma levels before and after the addition of benzodiazepines does not quite reach the 5% level of statistical significance.

Weighted mean phenytoin plasma levels were also calculated for 99 patients who had never received benzodiazepine drugs and 25 patients who had received these additional drugs. The phenytoin plasma levels for the latter 25 patients used for our calculations were those measured only while these patients had been taking chlorthalidone or diazepam for at least six weeks. The averages of the weighted mean phenytoin plasma levels were very significantly higher in patients who had been given chlorthalidone or diazepam than in those not taking one or other of these additional drugs (Table II). This difference was observed on two dosage schedules (300 mg and 400 mg per day) of phenytoin. Some patients were at one time receiving drugs other than phenytoin or a benzodiazepine, but there were no significant differences in the use of other drugs between the groups of patients

considered in this study.

These observations strongly suggest an interaction between phenytoin and benzodiazepines such that phenytoin intoxication may be precipitated by prescription of the latter drugs.—We are, etc.,

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¹ Kutt, H., and McDowell, F. J., *Journal of the American Medical Association*, 1968, 203, 969.

² Vajda, F. J. E., Abernethy, M. H., and Prineas, R. J., in press, 1970.

³ Wallace, J. E., *Analytical Chemistry*, 1968, 40, 978.

Infectious Mononucleosis

SIR,—The epidemiology of infectious mononucleosis (2 January, p. 58) has been of some interest to me in view of my medical care of 250 nursing staff. Of ten cases of Paul-Bunnell-positive glandular fever in the last three years none occurred within four months of entering the nurses' home, and there was no particular time after admission when the affliction was common. Since the average length of stay in the home is three years the incidence of infection is 4%. The age of the patients at the time of illness was between 18 and 24 years; there was no particular seasonal predilection, and all cases were sporadic and not associated with illness in their friends of either sex. There was very little oral osculation indulged in and no evidence to support Hoagland's hypothesis¹ that this is the principal method of spread of the disease.

The tendency of the disease to occur in institutions may be solely due to the frequent residence of the age group prone to the disease in such places. Among such nurses there was nothing to suggest that the disease had been acquired on vacation, which was usually in the summer. All available evidence seems to suggest that this sporadic form of glandular fever is not an acute infectious disease. It is possible that there is a "slow virus," which remains dormant until this particular period of life, when some alteration of immunity occurs, perhaps due to other infections.

The form of illness was fairly classical, but in two cases it was not until the end of the second week that the Paul-Bunnell test became positive. The degree of malaise is quite out of keeping with the degree of fever and sore throat, though in one nurse a temperature of 40° C. was recorded.—I am, etc.,

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¹ Hoagland, R. J., *American Journal of the Medical Sciences*, 1960, 240, 21.

Small Drumsticks and Long Y Chromosomes

SIR,—Davidson and Smith¹ demonstrated the presence of drumsticks in polymorphonuclear leucocytes of females. Subsequent studies have confirmed the relation between drumsticks and number and size of X chromosomes.² We report here the unusual observation of drumstick-like appendages in healthy males carrying a very long Y chromosome.

TABLE I—Phenytoin Plasma Levels in Individual Patients on the Same Dose of Phenytoin Before and After the Addition of a Benzodiazepine Drug to their Treatment

Patient	Dose of phenytoin (mg/day)	Plasma phenytoin levels (weighted means* in µg/ml)	
		Before benzodiazepines	After addition of benzodiazepines
A	400	14.6	19.5
B	400	19.8	41.2
C	400	11.2	13.6
D	300	10.4	15.5
E	300	4.1	11.8

For difference in levels before and after addition of benzodiazepines 0.1 < P > 0.05

*See text.

TABLE II—Phenytoin Plasma Levels in Patients taking Phenytoin and Receiving or not Receiving Additional Benzodiazepine Therapy

Daily dose of phenytoin (mg)	Therapy	No. of patients	Phenytoin plasma level—average of weighted* means (± S.D.)	Significance of difference
300	Taking benzodiazepines	8	13.1 (± 11.0)	P < 0.02
	Not taking benzodiazepines	48	7.2 (± 4.7)	
400	Taking benzodiazepines	17	18.8 (± 15.2)	P < 0.005
	Not taking benzodiazepines	51	10.6 (± 5.7)	

*See text

An apparently normal male (aged 17 years) was referred to us for routine haematological investigations before having a surgical correction of his nasal septum deformity. While examining a blood smear for a differential white cell count, drumstick-like appendages, about $1\ \mu\text{m}$ in diameter (Fig. 1a) were noted in 25% of

FIG. 1—Polymorphonuclear leucocytes with small drumsticks, (a) propositus (b) father.

polymorphonuclear cells. This finding led us to suspect the presence of a sex chromosome abnormality. Chromosome preparations from a blood culture revealed the presence of an unusually long Y chromosome, the size of a D (13-15) chromosome (Fig. 2). The karyotype was otherwise numerically and structurally normal. Barr bodies were absent in nuclei of the buccal mucosa.

FIG. 2—Comparison of D (13-15) chromosomes and the long Y chromosome of the propositus.

Examination of blood smears of the healthy father and two paternal uncles of the propositus revealed the presence of small drumsticks in polymorphonuclear leucocytes (Fig. 1b) with a frequency of 26%, 18%, and 29% respectively. Chromosome analyses from blood cultures showed the presence of the same abnormally long Y chromosome, as in the propositus.

Blood smears of the four subjects, fixed in methanol and stained with quinacrine hydrochloride³ showed a brightly fluorescing body in all types of leucocytes. About 90% of polymorphonuclear cells displayed the bright body either as a small drumstick, or as a sessile nodule, or as an intranuclear body (Fig. 3). Chromosomes of the four subjects, stained with quinacrine, showed a

FIG. 3—Polymorphonuclear leucocytes with brightly fluorescing nuclear bodies, (a) and (c) propositus; (b) and (d) father.

FIG. 4—Metaphase of the father with brightly fluorescing long Y chromosome.

bright fluorescence on the long arm of the Y chromosome, with the exclusion of a short segment near to the centromere (Fig. 4).

We conclude that in these subjects the small drumsticks are formed by the long Y chromosome. Y-specific nuclear appendages in polymorphonuclear leucocytes could be an isolated phenomenon limited to the family studied by us; it may be, however, that similar findings are observable in other individuals carrying very long Y chromosomes.

Our observation is a further illustration of the fact that study of nuclear morphology of polymorphonuclear leucocytes in relation to sex chromosome abnormalities is very worthwhile.—We are, etc.,

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- Davidson, W. M., and Smith, D. R., *British Medical Journal*, 1954, 2, 6.
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Heel Cushion for Use on the Operating-table

SIR,—I was interested in the de luxe method of relieving the pressure on the calf veins by means of heel and thigh cushions described by Mr. T. G. Wadsworth (19 December, p. 741). I notice that the illustration shows a patient lying on a Barts ribbed mattress and I might point out that the small bolster supplied with this mattress is intended to be placed under the Achilles tendons and thus in a very humble way performs the same function as the cushions described.¹ The height of the bolster was calculated to take most of the weight off the calf without hyperextending the knee joints. Similarly the middle bolster was designed to preserve the normal lordosis of the lumbar spine and thus reduce postoperative backache.² It is true that the Barts mattress was primarily designed to maintain a safe Trendelenburg position by skin friction only, but it is also extensively used in the horizontal position³ and it seems a pity not

to take advantage of its various functions.

Statistics for the effectiveness of the many prophylactic measures against venous thrombosis and pulmonary embolism are conflicting but my impression is that weight reduction on calf muscles does have a beneficial effect and this would be expected from the reasons set out so admirably by Mr. Wadsworth.—I am, etc.,

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Unusual Treatment of Paroxysmal Tachycardia

SIR,—Attacks of paroxysmal tachycardia result in lowering of the blood pressure because of cardiac insufficiency, and thus may cause cerebral, myocardial, and renal ischaemia, and even thrombosis or gangrene of the limbs. These possible serious consequences make effective emergency treatment vital, and this is usually achieved by simple methods of vagal stimulation. An unusual method of vagal stimulation, where others had failed, is described. The patient was a woman in whom the well-known manoeuvres of vagal stimulation gave no result, who improved on being put in the inverse vertical position—head down, legs up.

A woman of 48 years was admitted as an emergency with dyspnoea, palpitation, precordial pain, and anxiety. The clinical diagnosis, confirmed by electrocardiography, was supraventricular paroxysmal tachycardia. She had had such attacks for more than 20 years. The classical manoeuvres of vagal stimulation as well as the administration of quinidine had had no effect. The present attack had lasted 12 hours although the patient had been given, up to the moment of observation, 1.2 mg of intravenous Lanatosid C (extract of *digitalis lanata*). The blood pressure had dropped from 120/80 to 80/50. In desperation a new reflex method was tried. The patient was put completely upside down for 3 seconds and the disorder of rhythm disappeared almost instantaneously.

As it is known that attacks of paroxysmal tachycardia may be provoked by a sudden change in position of the body, we used this fact to obtain the opposite effect in our patient by a sudden and as radical as possible change of body position and consequently of circulatory conditions. When brought back to normal head up feet down position her pulse was 80/min and the clinical phenomena had disappeared.

This method has been the only effective procedure for this patient and has worked on subsequent occasions. Its effect may be explained by reflex circulatory modifications resulting in a better blood supply to the nerve centres and the myocardium, as well as to the heart's conduction system.—I am, etc.,

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