24-Hour Urinary Excretion of Hormones in Four Men with Gynaecomastia (a) when on Drug (b) when off Drug

Patient Drug	17-Oxosteroids (mg)		17-Oxogenicsteroids (mg)		Oestrone (μ g)		Luteinizing Hormone (IU)	
	On Drug	Off Drug	On Drug	Off Drug	On Drug	Off Drug	On Drug	Off Drug
Case 1 (diethylpropion) ..	34.6	12.9	23.6	10.3	25.1	12.3	60	17
Case 2 (diethylpropion) ..	14.1	8.6	12.3	6.7	19.2	nil	46	18
Case 3 (spironolactone) ..	12.0	15.1	11.0	10.6	7.9	13.5	12	30
Case 4 (spironolactone) ..	2.2	10.9	3.0	12.6	4.1	19.6	3	15
Normal adult male range	10-20		3-12		0-15		10-30	

(Apisate) one tablet daily for six months. After taking the drug for three months he developed right-sided gynaecomastia. Investigations, as outlined in case 1, were normal. The hormone levels returned to normal (see table) and the gynaecomastia improved after the drug was stopped.

Case 3.—This was a man aged 57 years who had seropositive anodular rheumatoid arthritis controlled with salicylates. He developed congestive cardiac failure, which was controlled with frusemide 80 mg and spironolactone 75 mg daily. After two months' therapy he developed well-marked gynaecomastia, which regressed rapidly after the spironolactone was stopped. All hormone levels except those of 17-oxogenicsteroids increased (see table) when the spironolactone was stopped.

Case 4.—This was a man aged 52 years who had the nephrotic syndrome. After one year's treatment with frusemide and spironolactone 75 mg daily he developed bilateral gynaecomastia associated with loss of libido. These improved when the spironolactone was stopped and also the excretion of hormones rose (see table).

In all cases 17-oxosteroids, 17-oxogenic steroids, oestrone, and luteinizing hormone were estimated from 24-hour urine collections during and after the drug administration. Urinary oestrone and luteinizing hormones were measured by the standard methods.^{1,2}

There can be little doubt that the diethylpropion and spironolactone were responsible for the gynaecomastia in these cases. However, the relationship to urinary luteinizing hormone and oestrogen levels are completely different. Those patients who were taking diethylpropion produced high levels which returned to normal after stopping the drug. This suggests that diethylpropion exerts a direct stimulatory effect on the hypothalamus and via luteinizing hormone releasing factor promotes the secretion of luteinizing hormone. Consequently the interstitial cells of the testis produce increased quantities of testosterone and oestrogen. Diethylpropion is a 1-phenylaminopranone and is an anorectic drug which is thought to exert a direct influence on the hypothalamus.³ Similarly, the amphetamines, which are known to cause gynaecomastia,⁴ exert an effect on the hypothalamus.⁵ An association between diethylpropion and gynaecomastia has not previously been reported, but it may have been overlooked—particularly as swelling of the breasts is a feature of obesity.

Luteinizing hormone and oestrogen levels were depressed by spironolactone. Spironolactone has a steroid structure and is a well-known cause of gynaecomastia.⁶⁻⁸ Investigation of the effects of spironolactone on the production of steroid hormones other than aldosterone have shown decreased urinary excretion of 17-hydroxycorticosteroids and 17-ketosteroids.⁹ Others have found a fall in plasma testosterone and urinary 17-ketosteroids but no appreciable change in the plasma androstenedione or the urinary 17-hydroxycorticosteroids, and suggested that spironolactone therapy was associated with a decreased secretion of testosterone from the testis.¹⁰ However, in these previous studies gonadotrophin levels were

not measured. In view of the low levels of luteinizing hormone and oestrogens recorded in the two cases presented it may be reasonable to assume that spironolactone caused suppression of gonadotrophin release and that its effect on the breast is a direct one.—We are, etc.,

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Contraception and Young People

SIR,—As a family planning doctor (F.P.A. clinic and N.H.S. hospital family planning service) may I comment on the correspondence about contraception and the young? In the experience of many clinic doctors the request for contraceptive advice comes from the young people who are already sexually experienced. Asking for contraception comes after the establishment of a sexual relationship. We do not endeavour to push them into sexuality but to help them to make responsible decisions and more mature relationships. Ideas and feelings about parents, marriage, and family life are discussed. This counselling may include contraception, which is usually a more realistic prevention of undesired pregnancy than saying "stop it."

A pregnancy may only complicate a situation of turmoil and immaturity and involve not only the girl's life but many others—perhaps for a life time. Those girls under 16 who do attend clinics are often accompanied by their mothers or other responsible adult. There are very few of them compared with the numbers we see on the hospital wards. These girls unfortunately have counselling from the doctor only after the termination of a pregnancy or the delivery of a baby. Many of us who work in this field feel that contact with a doctor who listens and tries to understand can be a therapeutic experience and fulfils a need which is not created by politicians or associations but part of human experience.—I am, etc.,

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Disability and Coal Workers' Pneumoconiosis

SIR,—Dr. Dewi Davies's recent communication (22 June, p. 652) in which he offered some speculative observations on the effects of simple pneumoconiosis also contained some misleading statements about the work of the pneumoconiosis medical panels. He suggests that heavy dust exposure may cause bronchitis. Though some correlation between the two appears to have been shown in Pennsylvanian coal miners^{1,2} a significant relationship has not been found by other workers.³⁻⁷ The major factor in the production of chronic obstructive bronchitis is cigarette smoking, and though there is some evidence that inhalation of coal dust may increase the effect of smoking this appears to be of minor significance. By contrast, the relationship of duration of dust exposure to radiographic category of simple pneumoconiosis and to dust content of the lungs is established.⁸⁻¹¹ Yet no correlation between chronic bronchitis and category of simple pneumoconiosis appears to exist.^{4,12}

Dr. Davies goes on to suggest, on the basis of recent studies of the behaviour of compact particles inhaled into human lungs, that chronic bronchitis may prevent the development of coal pneumoconiosis. It has been shown that such particles penetrate less to the non-ciliated airways in smokers with or without bronchitic symptoms than in non-smokers.¹³⁻¹⁵ More recent work appears to confirm that the penetration of small particles (2 μ m) into the periphery of the lungs is reduced in chronic obstructive bronchitis. But why should this point be raised by Dr. Davies if not to imply that "bronchitis"—presumably obstructive bronchitis—may result from coal dust exposure? While it can readily be agreed that coal dust exposure is unlikely to be beneficial to bronchitic subjects it has not (as we have just noted) been shown, in the absence of cigarette smoking, to be a significant factor in causing chronic obstructive bronchitis. Most observers have not found any significant correlation between impairment of FEV₁ and FVC and category of simple pneumoconiosis,^{3,4,16} though Rogan *et al.*¹⁷ recorded a small reduction in FEV₁ with cumulative exposure to coal dust. Dr. Davies suggests that such tests are inappropriate in estimating the degree of respiratory disability in simple pneumoconiosis because it has been claimed that disturbance in small airways function may occur early in the development of pneumoconiosis which is not detected by these tests. This applies equally, however, to impairment of gas transfer, alteration of residual volume, lung mechanics, pulmonary hypertension, and hypoxia, which have also been reported in some cases of simple pneumoconiosis. It has been pointed out¹⁸ that inferences drawn from tests used to measure small airways function may not be valid. Furthermore, there is no satisfactory evidence that the degree of impairment observed in the other functional parameters is associated with respiratory disability.¹⁹⁻²¹ No relationship has been found between the zones of lung fields predominantly involved in simple pneumoconiosis and ventilatory capacity.²² The question of respiratory disability in coal miners has already been accurately summarized elsewhere.²³

Dr. Davies is critical of some other aspects of the panels' work. Before they give an

opinion about whether pneumoconiosis causes or materially accelerates death the doctors of the panels study the pathologist's report and examine the relevant organs. They also consider the terminal illness and the mode of death, which are available in most cases. Furthermore, they usually have a record of the deceased's health over many years. They are thus able to judge the presence of chronic bronchitis and its influence on the cause of death. There are no other physicians in the country who possess the panels' unique experience and opportunity of comparing their findings during life with the appearance of the lungs after death. This experience is based on about 20,000 clinical examinations and 4,000 post-mortem examinations annually. The panels have requested that the lungs be perfused before examination, and the Association of Clinical Pathologists issued a leaflet in 1971 advising this and its recommendation was endorsed by the Brodrick Committee.²⁴ Differences of opinion between the coroners' pathologists and the panels are not frequent.

Dr. Davies's attitude to the panel is somewhat ambivalent, for while conceding that membership of it can bring enormous experience of the pathology of pneumoconiosis he criticizes panel members for lack of experience. The doctors of the panels are not expected to become competent pathologists overnight. When newly appointed they examine necropsy material with an experienced colleague, often in the presence of the pathologist, and thus become familiar with the morbid anatomy of the pneumoconioses. Opinion on the cause of death is given not by one but by two doctors. We acknowledge the debt of gratitude owed to our colleagues in the N.H.S., especially to pathologists, chest physicians, and others who, in general, appreciated that the panel doctors are clinicians who have a difficult job to do under circumstances which are sometimes ill-understood and misrepresented.—We are, etc.,

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Propranolol in the Treatment of Migraine

SIR,—The paper, "Propranolol in the Treatment of Migraine," by Drs. T-E. Widerøe and T. Vigander (29 June, p. 699) prompts me to report two patients in whom I suspect propranolol to be a precipitating factor of classical migraine.

Both patients were receiving the drug for the treatment of hypertrophic obstructive cardiomyopathy. The first, a boy of 19, started propranolol 40 mg three times a day in March 1972 and two weeks after the dose was increased to 80 mg three times a day he developed classical migraine for the first time. Clonidine 50 µg daily reduced the frequency and severity of attacks, though they persist. The second patient, a woman of 48, similarly had never previously experienced migraine and there was no family history of the disorder. She started propranolol 10 mg four times a day in February 1972 and this was increased by stages to 80 mg three times a day in June 1973. In April 1974 she presented after four episodes of vascular headache associated with teichopsia and left-sided sensory disturbance. Clinical examination, E.E.G., and brain scan were normal and she has had no further symptoms following the exhibition of clonidine 25 µg twice daily.

Eight patients with hypertrophic obstructive cardiomyopathy on propranolol attend the clinic. A much larger group with

ischaemic heart disease and arrhythmias are on beta-blocking drugs—mostly practolol or oxprenolol—and I am not aware of migraine presenting for the first time in this group.—I am, etc.,

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Smoking and Venous Thrombosis

SIR,—The papers by Dr. A. J. Handley and Mr. D. Teather (27 July, p. 230) and by Dr. P. Marks and Dr. P. A. Emerson (p. 232) show that non-smokers have a significantly higher incidence of venous thrombosis in the legs after myocardial infarction than smokers.

We have studied the prophylaxis of leg-vein thrombosis in 203 patients who underwent major surgery, were monitored by the ¹²⁵I uptake test, and whose smoking history was recorded. The original purpose of this trial was to compare a group on low-dose subcutaneous heparin, another receiving electrical calf-muscle stimulation, and a control group. The trial will be reported fully elsewhere.

The overall results in these 203 patients show no significant difference in the incidence of postoperative leg-vein thrombosis between smokers and non-smokers (see table I). Only 19, however, were operated on as emergencies, and probably the status of a patient who has had a myocardial infarct may be likened to that of a patient operated on for an acute illness rather than as an elective procedure. In the 19 emergency operations there was a higher incidence of postoperative leg vein thrombosis among non-smokers (see table II). The figures are, of course, too small for statistical analysis, but if the series were extended the difference might well become significant.—I am, etc.,

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TABLE I

	Smokers			Non-smokers		
	Total	Leg Vein Thrombosis	%	Total	Leg Vein Thrombosis	%
Control	33	12	36.4	55	24	43.6
Calciparine	24	4	16.7	36	2	5.6
Stimulator	21	7	33.3	34	12	35.3
Total	78	23	29.5	125	38	30.4

TABLE II

	Smokers			Non-smokers		
	Total	Leg Vein Thrombosis	%	Total	Leg Vein Thrombosis	%
Acute						
Control	2	1	50.0	8	4	50.0
Calciparine	3	0	0	0	0	0
Stimulator	3	1	33.3	3	2	66.7
Total	8	2	25.0	11	6	54.5
Non-acute						
Control	31	11	35.5	47	20	42.5
Calciparine	21	4	19.0	36	2	5.6
Stimulator	18	6	33.3	31	10	32.3
Total	70	21	30.0	114	32	28.1

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