Oral Contraceptives and Thromboembolic Disease

SIR,—Dr. J. Selwyn Crawford (11 May, p. 366) questions the conclusion that our study of thromboembolic disease in young women provides " . . . no suggestion . . . that venous thromboembolism tends to occur shortly after beginning the use of oral contraceptives." He suggests that this statement is incompatible with our observation that 42% (11 out of 26) of the women who developed thromboembolic disease and who were using oral contraceptives had been taking them for less than six months. If, however, the experience of the control women who were using oral contraceptives is also taken into account—4 out of 10 of whom had been using them for less than six months—we cannot see how these data can lead to any other conclusion.

It was noted by the Food and Drug Administration[1] that most of the reported deaths from thromboembolic disease associated with the use of oral contraceptives occurred within the first four months of administration, but it was also pointed out that this might well have been due to the differential reporting of events which occur soon after a new drug is prescribed. We agree that more information on this important aspect of the relationship between the use of oral contraceptives and venous thromboembolic disease is required, and this is one of the principal reasons why we are at present collecting information for the year 1967 to add to that for the years 1964–66.

Dr. Selwyn Crawford also asks, if the 11 cases of thromboembolism (not 10, as stated in his letter) occurring within six months of starting oral contraceptives are disregarded, do the remaining 15 cases constitute a significantly high incidence of the disease? The answer is yes. The appropriate comparison is then between 15 of 47 affected patients and 6 of 112 controls, and a difference of this magnitude would be expected to occur by chance less often than once in a thousand times.—We are, etc.,

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REFERENCE

1 *Food and Drug Administration Report on the Oral Contraceptives*, 1966. Advisory Committee on Obstetrics and Gynaecology, Washington, U.S.A.

Cardiac Catheterization in Cardiac Infarction

SIR,—Is cardiac catheterization a necessary or desirable investigation in acute cardiac infarction? Should this procedure be regarded as a routine investigation in cardiac units? These questions are even more apposite when the cardiac catheterization is not confined to the right side of the heart but includes also the left. The following recent publications have prompted me to raise this question.

Kirby *et al.*[1] reported their findings on two patients with acute myocardial infarction. The first patient had cardiac arrest during transport to hospital but responded to mouth-to-mouth respiration and external cardiac massage. When he arrived in hospital he had two bouts of ventricular fibrillation necessitating D.C. countershock. Then one catheter was passed via a femoral vein into his right atrium and another via the femoral artery into his left ventricle. Respiratory function tests were also done. He was described as "pale and semiconscious" when these tests were done. The other patient submitted to the same procedure was " pale, sweaty, and confused."

MacDonald *et al.*[2] reported the passing of three cardiac catheters, one into the pulmonary artery, another into the right atrium, and a third into the thoracic aorta on eight patients with recent cardiac infarction, one of whom was severely shocked and another was aged 79. The purpose of this experiment was to investigate the value of heroin in coronary thrombosis, and, for reasons not fully explained, the heroin was given directly into a heart chamber. The same authors[3] have also described an exactly similar experiment on another eight patients with recent cardiac infarction (one aged 70), but using pethidine instead of heroin.

A group of doctors from Hammersmith Hospital described[4] cardiac catheterization on 26 patients with acute myocardial infarction (age range 40 to 87). One patient was studied twice during successive infarcts. The special point of the investigation was that the cardiac catheter was left in situ in either the pulmonary artery or the right atrium for nine days, and to allow this to be done each had an infusion of one litre each day during this period.

If cardiac catheterization is not a routine procedure in coronary thrombosis then it must be deemed outside normal practice and thus experimental, and then special permission must be obtained after full explanation. This very question was posed in your section " Any Questions? " (1 July 1967, p. 37) and the following reply was given:

" In the vast majority of patients there is no indication for intracardiac catheterization after a myocardial infarction. Very occasionally, however, the question of surgical treatment of a complication such as a ruptured interventricular septum or mitral incompetence (due to malfunction of the papillary muscles) may arise. Under these circumstances cardiac catheterization and angiocardiography might well have to be performed to confirm the nature of the complication and to determine its severity."—I am, etc.,

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REFERENCES

1 Kirkby, B. J., McNichol, M. W., and Tattersfield, Anne, *Lancet*, 1968, **1**, 944.
2 MacDonald, H. R., Rees, H. A., Muir, A. L., Lawrie, D. M., Burton, J. L., and Donald, K. W., *Lancet*, 1967, **1**, 1070.
3 MacDonald, H. R., Rees, H. A., Muir, A. L., Lawrie, D. M., Burton, J. L., and Donald, K. W., *Lancet*, 1967, **2**, 863.
4 Fluck, D. C., Valentine, P. A., Treister, B., Higgs, B., Reid, D. N., Steiner, R. E., and Mounsey, J. P. D., *Brit. Heart J.*, 1967, **29**, 748.
5 *Brit. med. J.*, 1967, **3**, 37.

Electric Convulsion Therapy

SIR,—We must assume that your leading article (25 May, p. 448) was not written by a psychiatrist.

In spite of the advent of the tranquillizers, E.C.T. is still widely used in the treatment of schizophrenia, and in some cases is the treatment of choice.—We are, etc.,

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Vaccination Against Measles

SIR,—Dr. John F. Warin suggested that a booster dose of measles vaccine might be given routinely during pregnancy should future mothers fail to acquire sufficient antibodies from measles vaccination to protect their infants during the first nine months of life (13 April, p. 116). Nichols and others[1 2] have demonstrated chromosomal abnormalities in peripheral blood leucocytes of children with measles and to a lesser extent in subjects after immunization with measles vaccine. Though the full significance of these findings is not clear, it would seem wiser to avoid any routine vaccination during pregnancy.—I am, etc.,

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REFERENCES

1 Nichols, W. W., Levan, A., Hall, B., and Östergren, G., *Hereditas (Lund)*, 1962, **48**, 367.
2 Nichols, W. W., *Hereditas (Lund)*, 1963, **50**, 53.

Asbestos Bodies

SIR,—Your correspondents, Dr. W. J. Smither, of Cape Asbestos Company (6 April, p. 51), and Dr. H. C. Lewinsohn, of Turner Brothers Asbestos Company (13 April, p. 120), are correct in pointing out that I have no direct evidence that the " asbestos bodies " which I found in lung smears actually contain asbestos fibres (9 March, p. 614). The same criticism can be made of all similar previous studies. However, there is little evidence to support the suggestion that the bodies were produced by any of the alternative minerals proposed by Dr. Lewinsohn.

The bodies formed after inhalation of coal or graphite dust show a black central fibre or spicule, typical of the well-known " pseudoasbestos body," and such structures were specifically excluded from consideration in my survey.

As Dr. Lewinsohn admits, the bodies formed after exposure to talc dust may well be true asbestos bodies, formed from fibres of tremolite or anthophyllite in the talc, but when these are found in the lungs of talc workers they are accompanied by large amounts of doubly refractile dust particles.[1 2] None of the histological sections of lung in my series showed such accumulations. Since tremolite is usually present in talc only in small amounts, it is unlikely that a patient could inhale enough asbestos in this way to form detectable numbers of asbestos bodies without at the same time accumulating considerable amounts of talc dust in the lungs.

Formation of asbestos-like bodies has been demonstrated in experimental animals following inhalation of glass fibre, but it is by no means a consistent finding, in contrast with experimental asbestosis in susceptible species. Thus Schepers[3] and Gross *et al.*,[4] make no

mention of asbestos-like bodies in describing the effects in the lung of inhaled glass wool fibres in two animal species, including a species which consistently forms asbestos bodies when exposed to asbestos dust. There are few reports in the literature on the effects of glass fibre in man, but Murphy,[5] in a human case of "fibre-glass pneumoconiosis," describes and illustrates numerous uncoated glass fibres in the lung tissues without mentioning asbestos-like bodies. It is also likely that, as used in industrial conditions, much of the dust derived from glass fibres consists of particles too large to be respirable.[4] For these reasons I consider it is very unlikely that any of the "asbestos bodies" in my series can be attributed to glass fibres.

The role of diatomaceous earth is likewise doubtful. Vigliani and Mottura[6] describe in detail the post-mortem histological appearances in the lungs of a man exposed to pure calcined diatomite dust without mentioning asbestos-like bodies. That they were aware of the possibility of finding such bodies is clear from their reference to the work of Nordmann,[7] who described asbestos-like bodies in lung tissue at necropsy in patients exposed to diatomaceous earth and quartz dust. Nordmann, however, is careful to distinguish between "pseudoasbestos bodies" present in two of his six cases and "true asbestos bodies" found in another two cases known to have been exposed to asbestos as well as diatomaceous earth. Some of the "pseudo-asbestos" bodies he illustrates do not resemble asbestos bodies.

Filamentous aluminium silicate has been shown in hamsters to evoke the formation of asbestos-like bodies, but I do not know of any human case in which the presence of such bodies has been attributed to this material. Furthermore, I understand that aluminium silicate has only been used as an insulator in this country for about the last three years (and then only in small quantities for specialized purposes), and thus it also seems unlikely to be an important source of confusion in my survey. None of the histological sections in my series showed any evidence of haemosiderosis of elastic fibres.

By contrast, there is strong circumstantial evidence that many of the bodies I found are in fact true asbestos bodies. More than half of the patients for whom an occupational history is available had either worked with asbestos or had worked in an environment where incidental inhalation of asbestos at some time is virtually certain to occur. The fact that such evidence has been elicited by the comparatively crude methods employed in obtaining retrospective occupational histories from relatives of deceased patients suggests that occupational exposure is probably a more important source of asbestos fibres in the population than the general environmental contamination by asbestos suggested by previous writers.—I am, etc.,

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REFERENCES
1 McLaughlin, A. I. G., Rogers, E., Dunham, K. C., *Brit. J. industr. Med.*, 1949, **6**, 184.
2 Hunt, A. C., *Thorax*, 1956, **11**, 287.
3 Schepers, G. W. H., *Arch. industr. Hlth*, 1955, **12**, 280.
4 Gross, P., Westrick, M. L., McNerny, J. M., *Arch. industr. Hlth*, 1960, **21**, 10.
5 Murphy, G. B., *Arch. environm. Hlth*, 1961, **3**, 704.
6 Vigliani, E. C., Mottura, G., *Brit. J. industr. Med.*, 1948, **5**, 148.
7 Nordmann, M., *Virchows Arch.*, 1943, **311**, 116.

Genetics of Finger-prints

SIR,—The erudite and amusing article on finger-prints by Professor L. S. Penrose (11 May, p. 321) contains an idea which may prove to be of major importance to our understanding of the mode of action of chromosomes.

After presenting his findings that total ridge count of the fingers varies in inverse proportion to the number of sex chromosomes present the author states (p. 324): "The queer thing is that the effect is produced by the whole chromosome, or a large segment, rather than by its constituent genes." A few years ago I put forward a similar view to account for the process of sex differentiation: "there seems to be strong evidence that the inheritance of sex . . . is controlled not by individual genes but by whole chromosomes or at least large parts of chromosomes."[1] There is increasing evidence that the biological difference between males and females is basically a quantitative one,[2–5] and Professor Penrose's findings appear to support the view that genetically determined quantitative variation can be affected by entire chromosomes or large chromosomal sections.

Professor Penrose's studies emphasize the value of dermatoglyphics, for here we are dealing with a quantitative variable which is fixed in embryonic life and is subsequently unaffected by either environment or hormones. For this reason the sex chromosome constitution may be reflected more directly in ridge counts than in variables of more obvious biological and medical significance.—I am, etc.,

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REFERENCES
1 Mittwoch, U., *Nature (Lond.)*, 1964, **204**, 1032.
2 Parkes, A. S., *Brit. med. J.*, 1962, **2**, 71.
3 Mittwoch, U., *Sex Chromosomes*, p. 243, 1967. New York, London.
4 Mittwoch, U., *Nature (Lond.)*, 1967, **214**, 554.
5 Ohno, S., *Sex Chromosomes and Sex-linked Genes*, p. 167, 1967. Berlin, Heidelberg, New York.

Crohn's Disease and Carcinoma of Colon

SIR,—With reference to the article by Drs. A. D. Perrett, S. C. Truelove, and G. R. Massarella (25 May, p. 466), in which the authors report a possible association between the two diseases, they give seven references to reports of cases in which carcinoma of the small intestine developed in relation to pre-existing Crohn's disease of the ileocaecal junction. They omitted, however, reports by Martinelli and Belluci,[1] Steele and McNeely,[2] Almond *et al.*,[3] and Davis and Caley.[4] Since carcinoma of the small intestine is very rare, such reports would seem highly significant in pointing to the premalignant nature of Crohn's disease. In addition, Hughes,[5] case records of Massachusetts General Hospital, Case 43292,[6] and Wyburn-Mason[7] have reported cases in which Crohn's disease in the ileocaecal region developed into malignant lymphoma. One of my surgical colleagues also had a male patient of 55 years of age who developed intestinal obstruction due to a lesion in the upper part of the ileum, which was resected with end-to-end anastomosis. Sections of the lesion showed the typical changes of Crohn's disease. Seven years later intestinal obstruction recurred and laparotomy now showed a tumour at the site of the anastomosis. Histologically this proved to be a reticulosarcoma. Such observations lend weight to the suggestion that Crohn's disease may be a premalignant condition.—I am, etc.,

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REFERENCES
1 Martinelli, V., and Bellucci, M., *Ann. ital. Chir.*, 1959, **36**, 557.
2 Steele, D. C., and McNeely, D. T., *Canada med. Ass. J.*, 1960, **83**, 379.
3 Almond, C. H., Neal, M. P., and Moedl, K. R., *Missouri Med.*, 1960, **57**, 452.
4 Davis, A., and Caley, J. P., *Postgrad. med. J.*, 1960, **36**, 380.
5 Hughes, R. K., *Amer. Surg.*, 1955, **21**, 770.
6 Case Records of Massachusetts General Hospital, Case 43292, *New Engl. J. Med.*, 1957, **257**, 135.
7 Wyburn-Mason, R., *A New Protozoon*, 1964. London.

Guanethidine and Diabetes

SIR,—Diabetes and hypertension are often found in the same patient. Although many patients with diabetes must have received guanethidine for control of coexistent hypertension, we have been unable to trace any direct reference to the effect of guanethidine on clinical severity or insulin dosage in diabetic patients. An inquiry to the manufacturers of guanethidine revealed the same lack of published data in this regard. This prompted us to record briefly the following case, where a striking increase in insulin requirements and a rise in blood sugar levels was noticed when guanethidine was discontinued in a diabetic patient.

A 43-year-old housewife was a known diabetic for the last 14 years. Her fundi showed advanced diabetic retinopathy, and she had gradually lost vision over the last three years with development of retinitis proliferans in the right eye. She has been taking soluble insulin 40 units twice daily since 1964, and was quite well controlled. She developed the nephrotic syndrome, with proteinuria, oedema, hypercholesterolaemia, and her blood pressure, which was 150/90 in 1964, gradually rose to 210/120 in June 1967. She was started on bendrofluazide 5 mg. daily and methyldopa 250 mg. three times a day, which was replaced by guanethidine 10 mg. twice daily in December 1967. She needed a little less insulin after this, and was well controlled on soluble insulin 40 units in the morning and 30 units in the evening. She was admitted on 1 March 1968 with a history of several fainting attacks over the previous week. Her blood pressure on admission was 200/100 lying, and 120/80 standing. Her blood sugar was 220 mg./100 ml. It was thought that the fainting might have been due to postural hypotension due to guanethidine, and this was discontinued on 5 March. A progressive increase in glycosuria was noted over the next few days, and she complained of increased thirst while on the same insulin dosage. Her insulin was increased by 8 units on 11 March. The blood sugar levels were found to have gone up in spite of this. On 13 March the blood sugar was 429 mg./100 ml. at 10 a.m. and over 500 mg. at 3 p.m. Insulin was increased by 8 units. On 16 March the blood sugars were 327 mg./100 ml. at 10 a.m. and 478 mg./100 ml. at 3 p.m. Insulin was further increased by 8 units on 19 March to 52 units in the morning and 42 units in the evening. Blood sugars on 20 March were 244 mg./100 ml. at 10 a.m. and 378 mg./100 ml. at 4 p.m. On 22 March these were 347 mg./100 ml. at 10 a.m. and 468 mg./100 ml. at 3 p.m.

Thus within a few days of discontinuing guanethidine the requirements of insulin had increased considerably. Since there was no