Familial antithrombin III deficiency

SIR,—The impressive family study of antithrombin III (ATIII) deficiency in the west of Scotland by Dr M Mackie and his colleagues (21 January, p 136) will stimulate the search for further examples. The incidence reported by them of clinical thrombotic disease in the deficient patients (7 out of 12) and its severity follow the patterns to be found in the literature cited. It is reasonable to assume that another thrombogenic factor may be present to account for those affected clinically. It is less likely that the ATIII-deficient persons who are unaffected have special protection. The recent study¹ in our laboratory of a smaller but similar family showed not only a lower rate of thromboses in the deficient (2 out of 9) but also an indication that hypertriglyceridaemia may have been the additional factor.

Deficiency of ATIII should provide a sensitive human model for the evaluation of thrombotic risk factors. Clearly these may not be the same in different families or even individuals, but it is logical to plan a comprehensive survey in any future study. Such knowledge will be of use in assessing the need for prophylaxis, which, as the authors state, is usually anticoagulation with warfarin. However, we are less certain about their suggested use of subcutaneous heparin in pregnancy. The decreased levels of ATIII found by Marciniak and Gockerman² in patients receiving full doses of heparin for at least three days were also found in our patient who rethrombosed shortly after being taken off heparin.³ Subsequently we have measured a fall in ATIII levels of between 12 and 41% in seven patients receiving minidose subcutaneous heparin for five days after myocardial infarction. This may not be important when the levels do not fall far below the normal range, but where the resting level is already 50% below normal the results may not be desirable and may account for the reported failures of heparin therapy in this condition. It is true that if, in addition to heparin, the necessary volume of plasma can be given sufficiently often to raise the level of ATIII this potential danger will not arise. The possibility of producing a plasma concentrate⁴ may prove to be the answer in this high-risk group.

O H B GYDE
W A LITTLER
D E STABLEFORTH

Department of Haematology,
East Birmingham Hospital,
Birmingham

¹ Gyde, O H B, *et al*, *British Medical Journal*. In press.

² Marciniak, E, and Gockerman, J P, *Lancet*, 1977, 2, 581.

³ Fiskens, R A, *et al*, *Lancet*, 1977, 2, 1231.

⁴ Wickerhauser, M, personal communication.

SIR,—The recent report by Dr M Mackie and others (21 January, p 136) of a Scottish family with familial antithrombin III (AT III) deficiency prompts us to report the first English family with the same condition. A mother and three of her four sons, living on the south coast, are affected.

The mother's AT III level measured by functional assay¹ is 51% and by immunological assay² 54%. She is reported to have had deep vein thrombosis (DVT) after every pregnancy and has recently developed a spontaneous axillary vein thrombosis. Three sons have AT III levels of 48%, 55%, and 56% (functional) and 50%, 55%, and 37% (immunological), respectively, while levels of α_1 -antitrypsin and α_2 -macroglobulin were found to be within normal ranges. These sons have all had

recurrent DVT and have grade IV post-phlebotic legs. One son has, in addition, also had an inferior vena cava thrombosis (age 8) and mesenteric thrombosis (age 30). The father, a maternal aunt, and the fourth son and his son are asymptomatic and all have AT III levels above 80%.

The typical clinical presentations are demonstrated by this small family, but the inferior vena cava thrombosis developing at the age of 8 years in one member illustrates that symptoms may not be confined only to adulthood. Mendelsohn³ has reported multiple thrombotic events in an 8-month-old infant with an AT III deficiency. Furthermore, familial AT III deficiency may not be as rare as is currently thought. Since we have started screening patients with strong family histories of venous thrombosis we have uncovered several subjects with low AT III levels and their families are now under investigation. It is our policy to recommend self-administered low dose subcutaneous heparin for all confirmed cases.

H A DE HAAS
M F SCULLY
S E CLARK
V V KAKKAR

Thrombosis Research Unit,
King's College Hospital Medical School,
London SE5

¹ Scully, M F, and Kakkar, V V, *Clinica Chimica Acta*, 1977, 79, 595.

² Fagerhol, M H, and Abilgaard, U, *Scandinavian Journal of Haematology*, 1970, 7, 10.

³ Mendelsohn, G, Gomperts, E D, and Gurwitz, D, *Thrombosis and Haemostasis*, 1976, 36, 495.

Regional variations in incidence of urinary stones

SIR,—The letters from Dr B T Williams (28 January, p 233) and Dr M J McCarthy (p 234) commenting on our paper (14 January, p 67) again raise the question of the extent to which regional differences in provision of hospital beds nullify the use of hospital admission rates as comparative indicators of disease incidence. The degree to which admission rates reflect incidence varies from one disease to another. At one extreme patients with perforated peptic ulcers will be admitted to hospital irrespective of the number of available beds, and hospital admission rates will therefore be a measure of incidence. At the other extreme regional admission rates for non-infective skin disease show a high correlation with total numbers of dermatological beds available and the admission rates cannot be taken as indicators of incidence. Dr Williams speculates that emergency admission for renal stones and renal colic may correspond to the latter. He thereby implies that many of the patients admitted as emergencies to hospitals in southern England would, had they lived in the north of England, be looked after at home by their general practitioners.

Dr Williams's suggestion arises from the correlation (coefficient=0.44) between numbers of surgical and urological beds per 100 000 population and emergency admission rates for renal stones and colic. However, numbers of beds are a poor indicator of actual availability of beds for emergency admissions because bed availability is critically influenced by patients' average duration of stay in hospital. Moreover, the low correlation coefficient of 0.44 implies that at most only 20% of the variation in admission rates is explained by variation in numbers of beds. (Likewise the correlation coefficient of 0.49 between total surgical beds and all admissions for appendicitis, which Dr Williams cites, shows that at most only 25% of the variation in appendicitis is explained in this way.)

Dr Williams suggests that the summer peak in emergency admission for renal stones and colic may merely reflect increased availability of surgical beds during the summer. He writes that "during the winter months, especially in the less well-resourced regions, surgical beds have to be 'borrowed' to cater for the increased demand from patients suffering from serious acute medical conditions such as pneumonia." However, our data show that the variation in winter and summer admission rates is similar in extent in all regions, irrespective of the numbers of beds. We think his suggestion is unlikely to be true.

Dr McCarthy states that regional variations in appendicitis admissions are similar to those for renal stones. This is incorrect. The statement is based on admission rates for appendicitis quoted in the reports of the Hospital Inpatient Enquiry (HIPE). The correlation coefficient between appendicitis admissions in the most recent report, that for 1973, and the emergency admission rates for renal stones and colic cited in our paper is only 0.24. This falls to 0.08 if the analysis is restricted to admission rates for acute appendicitis—that is, patients coded as acute appendicitis who were admitted as emergencies and operated upon (unpublished data). This points to the need for detailed analyses of HIPE data when making inferences about incidence rather than basing conclusions on the summarised data presented in published tables.

Confirmation of our conclusion that there is a higher incidence of renal stones in southern England can come only from a special survey. We agree with Mr R Scott and Dr S Ljunghall (18 February, p 439) that a survey is necessary and feasible. Two such surveys, into Paget's disease of bone¹ and Perthes's disease of the hip,² have recently been completed in this department. For both diseases HIPE data would be predicted to be inappropriate as indicators of incidence or prevalence. Yet the findings of the surveys confirmed for each disease the suggestion from HIPE analyses of a higher frequency in the north-west of England than the south.

To dismiss hospital admission rates as indicators of geographical differences in disease incidence within Britain is to take too superficial a view. Although, as we stated in our paper, biases such as those produced by regional differences in hospital admission practice cannot be eliminated, we nevertheless think that detailed analyses of HIPE data are a useful preliminary in geographical studies of disease incidence.

D J P BARKER
S P B DONNAN

University Department of
Community Medicine,
Southampton General Hospital,
Southampton

¹ Barker, D J P, *et al*, *British Medical Journal*, 1977, 1, 1181.

² Barker, D J P, Paper read to meeting of Society for Social Medicine, Birmingham, September 1977.

Duration of immunity conferred by rubella vaccines

SIR,—The short reply in your Any Questions column (3 December, p 1466) on the duration of immunity provided by rubella vaccines implies that it is only a matter of time before studies confirm that vaccination confers life-long protection. Your expert also wrongly implies that all vaccine strains are equivalent or that the strains of vaccine principally used in vaccination programmes in the United States and Great Britain are the same. Many studies have shown that the immediate antibody responses elicited by vaccination differ with strains¹⁻⁴ and others⁵⁻¹³ indicate