Mortality related to thrombosis in congenital antithrombin III deficiency.

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inactivated tumour-suppressor genes This may lead to uncontrolled cell division and malignant transformation

An increasing number of epidemiological studies support the Fathalla hypothesis Fathalla noted that pregnancy suppresses ovulation and protects against ovarian cancer The protective effect increases with increasing parity Oral contraception inhibits ovulation and is also associated with decreased risk of ovarian cancer [4] This reduction is related to the length of use of oral contraception Furthermore the incidence of ovarian cancer peaks after the menopause and completion of maximum ovulatory cyclical damage Cruickshank[5] has predicted that because ovulation occurs more often in the right ovary, one might expect ovarian cancer to develop more commonly on the right side In a study of women with epithelial ovarian cancer in Scotland, he found this to be so, with more tumours in the right ovary than the left [5]

In an independent review of risk factors Pike[6] stated that the major impetus to cell replication is repair of the epithelial surface after ovulation He noted that each month cells divide to seal the hole and added, "not that cell division itself causes cancer, but whatever does is made worse by cell division" Henderson and Preston-Martin[7] noted that the division of cells that would usually not be replicating may be especially error prone because efficient repair mechanisms are absent Epidemiological evidence thus points to defective cellular repair after ovulation as a major risk factor in ovarian cancer The molecular evidence suggests that this may be attributable to inactivated tumour-suppressor genes, possibly the missing link in the Fathalla hypothesis

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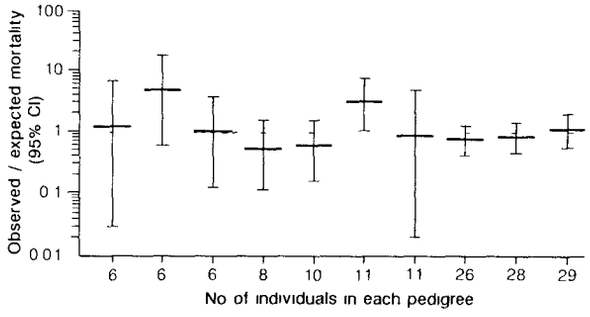
Mortality related to thrombosis in congenital antithrombin III deficiency

SIR,—Dr De Stefano and Dr Leone (April 6, p 847) comment on the results of our study on mortality in families with hereditary antithrombin III (AT III) deficiency (Feb 2, p 260), and discuss their own analysis of 37 families taken mainly from previously published accounts Whereas we found no excess mortality compared with the general population in 171 family members from 10 kindreds, their findings in 552 individuals with a high probability of deficiency were strongly suggestive of excess mortality from venous thromboembolism, although a direct comparison with the general population was not possible They speculate as to whether our findings might have been related to the inclusion of kindreds with mild clinical expression, and suggest that the use of anticoagulants as long-term prophylaxis in symptom-free individuals should be reconsidered

We believe that our approach is more likely to lead to a correct estimate of mortality in those with AT III deficiency than the method described by De Stefano and Leone because their conclusions were based on 34 pedigrees from published reports and 3 pedigrees from their own series As they point out, case-reports are likely to give a biased view, since pedigrees with remarkable features tend to be published We do not know if these reports gave complete pedigrees that were confirmed by genealogical investigations

Moreover, we do not believe that there may be two populations of AT-III-deficient kindreds, one with a high risk of (fatal) thromboembolism and one with a low risk Although, in retrospect,



Mortality according to family pedigree

some families seem to have experienced more episodes of thromboembolism than other families, this observation per se does not imply that one can predict a higher risk for individuals from these kindreds For type I deficiency, in which AT III activities are closely distributed around 50% of normal, differences in clinical severity are hard to imagine, unless one suggests a second heritable defect At present, there is no evidence for a second defect

With such reasoning in mind, we have repeated our analysis for the ten families separately (figure) Although some variation between families is present, we believe that this is probably because of chance variation, and not because of true differences in mortality associated with AT III deficiency In the three largest pedigrees, in which the most reliable estimates would be expected, no excess mortality is found

De Stefano and Leone rightly state that one of the aims of long-term prophylaxis should be to prevent not only mortality but also morbidity from venous thromboembolism Although our study was confined to mortality, anticoagulation has its own risk of morbidity and mortality, which may become substantial if treatment is continued for decades There is no evidence to date that, in symptomless patients, the benefits of anticoagulation on morbidity and mortality outweigh the risk of this treatment Until such evidence is available, we adhere to the principle of "*in dubio, abstine*"

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Hypotension with midazolam and fentanyl in the newborn

SIR,—Midazolam, a water-soluble benzodiazepine with a shorter elimination half-life than diazepam, has been proposed for sedation in children[1] and the newborn who need surgery or intensive care We report hypotension in six babies with respiratory distress syndrome who were given midazolam in the first 12–36 hours of life for sedation Direct or indirect blood pressure (BP) was recorded

Patient 1 received an intravenous infusion of 1 μg/kg/h fentanyl during the first 24 hours of life Because sedation was inadequate, fentanyl was stopped and immediately replaced by a 60 μg/kg/h midazolam infusion BP, which was already unstable (40/20 mm Hg), decreased 5 h later to 34/13 mm Hg, and heart rate fell from 134 to 115/min Echocardiography showed poor myocardial contractility Midazolam was stopped and dobutamine was initiated BP fell further and remained unmeasurable by external oscillometry for 1 h Flumazenil, a benzodiazepine antagonist, was administered However, systolic BP remained under 40 mm Hg and heart rate under 120/min for another 5 h

Patient 2 received an intravenous bolus of 1 5 μg/kg fentanyl and 5 h later a single intravenous bolus of 200 μg/kg midazolam was administered BP had been unstable 1 h after midazolam BP suddenly fell to 38/22 with a pulse of 110 and remained low for 7 h, despite dopamine and plasma