While these may not all have been statistically watertight studies, they did show a reduced rather than an increased incidence of thromboembolic disease. Hougie² in an excellent review article quotes the Puerto Rican study³ designed especially to determine the effects of oral contraceptive agents on the incidence of thromboembolic disease in which 9,898 patients were randomly allocated to the contraceptive pill or to other contraceptive methods and followed up. This very large prospective study also failed to show an increased risk of thrombophlebitis among pill users. It may be argued that these surveys are dealing with different population groups, but it is by no means proved that "clotting [is] provoked by oral contraceptives."—I am, etc.,

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Anaemia in Beta-thalassaemic Carriers

SIR,—We are very interested in the question of anaemia occurring in heterozygous beta-thalassaemic subjects. Thus we are grateful to Dr. H. H. M. Knox-Macauley and his colleagues (21 July 1973, p. 150), who report a reduced haemoglobin level in beta-thalassaemic carriers. Two of us had already reported similar results in heterozygous beta-thalassaemic children of both sexes.¹ Nevertheless, we think that neither report proves whether symptomless beta-thalassaemic subjects are anaemic or not, since the study of Dr. Knox-Macauley and his colleagues was concerned with patients referred to hospital and ours related to a child inpatient population. Similarly, no conclusive evidence is provided by a recent investigation performed in Thailand,² since no information concerning the age of the subjects examined is given. We have therefore determined the haemoglobin levels of groups of symptom-free heterozygous beta-thalassaemic males (age 15–60 years) and females (15–52 years) compared with normal controls. The results are given in the table.

These data show a significant decrease in the mean haemoglobin level in beta-thalassaemic carriers of both sexes. According to one authority³ the lower limits of normal haemoglobin content at sea level (as in the present investigation) are 14 and 12 g/100 ml for males and females respectively. The haemoglobin level in 86 of the 87 beta-thalassaemic males examined by us was below 14 g/100 ml, while in 61 of the 70 beta-thalassaemic females it was less than 12 g/100 ml. Our study therefore leads to the conclusion that anaemia is quite a common finding in beta-thalassaemic carriers.

In our opinion this pattern of anaemia could be related to the reduced mean corpuscular haemoglobin content¹ brought about by a decrease of both alpha- and beta-chain production,⁵ with impaired haem biosynthesis⁶ and increased haemolysis.⁷—We are, etc.,

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Steroid Aerosols in Asthma

SIR,—The disturbing incidence of candida infections of the pharynx and the larynx reported by Dr. M. K. McAllen and others (2 February, p. 171) is not universal. I have treated 149 patients with an aerosol of beclomethasone dipropionate and in 80 the period of observation has been for 20–30 months.¹ In five cases sore throat, huskiness, or hoarseness was reported. In one case *Candida albicans* was grown but quickly disappeared with treatment with nystatin lozenges. The patient has continued for a further 12 months with a dose of 400 µg of beclomethasone daily without trouble. In the remaining four cases postnasal swabs were negative but symptoms disappeared after the dose of aerosol had been decreased to 300 or 200 µg per day. Despite careful questioning, none of the other patients has complained of a sore throat or hoarseness.

Other findings may be of interest. After 18 months of treatment with the aerosol five patients have been weaned completely without relapse of asthma, but in 25 others the symptoms recurred and they have had to continue, usually at a dose of 200–300 µg daily. Seventeen patients claim that they have had more frequent attacks of purulent bronchitis than before treatment; 11 have had to have occasional courses of oral prednisolone and antibiotics together, but have continued with good function between attacks. Four patients who had originally been well controlled have relapsed and failed to respond to further treatment and are maintained now on oral steroids. Originally 47 out of 75 patients who had been maintained on systemic steroids pre-

viously were weaned successfully from oral steroids and received at least equal benefit from the aerosol. Two only of these patients have relapsed and have had to resume oral steroids daily. No other untoward effects have been noted. Serum cortisol levels have remained normal in all patients who had not previously received oral steroids and in the 45 completely weaned successfully from oral steroids.

Regular use of the beclomethasone aerosol remains a significant advance in the safe management of asthma as long as (1) the dose is kept to the minimum required and (2) the patient is carefully instructed how to use the aerosol, otherwise most is expended in the mouth and throat.—I am, etc.,

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Clinical Diagnosis of Reye's Syndrome

SIR,—Your leading article on this subject (11 August, p. 308) is timely and emphasizes the need to consider Reye's syndrome in any child with an encephalopathy of no apparent cause.

Of great concern to clinicians in establishing the diagnosis of the disease are the guidelines advocated in your article, which are largely drawn from the prospective studies of Glasgow *et al.*^{1–3} In these studies of patients with encephalopathy and fatty visceral degeneration in Thailand no mention is made of the presence or lack of toxic quantities of aflatoxin in the urine of the patients or in the tissues in fatal cases. In a series of earlier articles from Thailand on the epidemiology, toxicology, and clinical study of a Reye's-like syndrome the toxin of *Aspergillus flavus* was implicated as the aetiological factor.^{4–7} A striking clinical, biochemical, and pathological corollary to the human disease can be produced in the juvenile monkey by the administration of a purified toxin derived from cultures of fungi contaminating foodstuffs ingested by victims.⁸

Clarification of this point about the presence or absence of toxic amounts of aflatoxin in the fluids and tissues of affected patients is of fundamental importance before criteria developed for the aflatoxin-related diseases are adopted for the diagnosis of a disorder not due to aflatoxins. Differentiation of these two syndromes can be made not only on toxicological grounds but also pathologically and clinically. While there are many similarities, clinical differences can be found, especially the precipitous course in the Thai disorder, which is often heralded by seizures, which progressed to status epilepticus in about 50% of one series of 67 cases.⁴ Hypoglycaemia is also more frequent in the Thai disease, being found in 75% in one series¹ and in 99% in another.⁴ In three of Glasgow *et al.*'s 43 cases consciousness was regained on administration of intravenous glucose^{1–3} and in several others improvement such as increased pupillary responses were seen. From these observations they concluded that hypoglycaemia played an important role in the development of the encephalopathy in their patients. The hypoglycaemia in Reye's syndrome is not influenced by infusions of

	No. of cases	Haemoglobin (g/100 ml) (mean ± S.D.)	P
Heterozygous beta-thalassaemic males	87	11.72 ± 1.29	
Control males	650	15.04 ± 1.33	<0.001
Heterozygous beta-thalassaemic females	70	10.62 ± 1.30	
Control females	261	13.38 ± 1.00	<0.001

glucose and is not associated with convulsions in all cases despite its severity.^{9,10} Pathologically, major differences can be found in the lungs and lymphoid tissue, which are grossly abnormal only in the aflatoxin-related disease.

The clear differentiation of these two disorders is a necessary prerequisite to the development of diagnostic criteria and perhaps of treatment. Until more specific biochemical parameters are identified the diagnosis of Reye's syndrome must rely on a number of clinical criteria which should at least include: (1) the presence of a progressive encephalopathy; (2) absence of known exposure to toxins or trauma; (3) normal cerebrospinal fluid (cells, culture, and protein); and (4) biochemical evidence of liver dysfunction without significant bilirubinaemia (either hyperammonaemia elevated twofold or prothrombin abnormality <70% of normal and evidence of elevation of liver enzymes >twofold). These biochemical parameters are clearly arbitrary but offer a reasonable chance of eliminating most toxic encephalopathies with hepatic involvement which are not Reye's syndrome. Further supportive evidence might be provided by the histological examination of the liver, but this may not be possible in patients with significant prothrombin abnormalities.

In order to avoid confusion, Reye's-like syndromes due to specific toxins should be identified as such. The use of the term toxic encephalopathy with fatty visceral changes due to a specific toxin, such as aflatoxin B₁, is preferable to the use of Reye's syndrome for disorders with identifiable aetiologies.—I am, etc.,

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Suicide by Private Pilots

SIR,—In your leading article on this subject (2 February, p. 168) you pose the question whether aviation medical examiners should be required to explore in some depth the psychological aspects of private pilots.

There are, of course, international standards of psychological fitness as well as physical fitness which private pilots must meet before being given a flying licence, and the fact that accidents from medical causes are rare by comparison with the other causes shows that the system of medical supervision is reasonably effective. The aviation industry is more conscious of cost-effectiveness than most others, and the above background has led the International Civil Aviation Organization (the United Nations standard-setting body) to conclude that only

relatively infrequent medical examinations of somewhat limited scope can be justified to meet the level of safety generally acceptable to the public—perhaps because private pilots more commonly kill only themselves in accidents.

Your timely leading article will remind aviation medical examiners—as we do at our annual seminars—of the background factors they should search for during routine medical examinations. I hope it will also remind doctors caring for patients under stress whom they know to be pilots that effective prevention of this type of accident lies almost entirely in their hands. The medical defence organizations are well aware of this problem and they or I would be happy to give suitably confidential advice on particular cases.—I am, etc.,

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Cholestyramine and Diabetic and Post-vagotomy Diarrhoea

SIR,—We were interested in the letters from Dr. T. S. Low-Beer and Dr. J. G. Allan and others (22 December, p. 741) and would like to make some further comments.

We have now treated five patients with persistent post-vagotomy diarrhoea with cholestyramine, bowel habit returning to the "pre-vagotomy norm" in all subjects. These findings confirm those of Ayulo¹ and are of particular interest in view of the increase in bile acid excretion demonstrated in post-vagotomy subjects by Dr. Allan and his colleagues.^{2,3}

Our theory of increased bile flow following vagotomy refers to patients in their natural feeding state and in whom acid and gastric contents are reaching the duodenum. Our assumption is based on the findings of Saburov,⁴ who showed that in dogs introduction of hydrochloric acid into the duodenum caused increased bile secretion and that vagotomy led to an even greater intensification of secretion by the same quantity of acid. Secretin and possibly other hormones may be involved in this increased bile flow.

The existence of a limited reabsorptive capacity of the small intestine for bile salts is suggested by the fact that feeding pure bile salts for a few days induces severe diarrhoea.^{5,6} Similarly Dr. Allan and his colleagues presented evidence of limitation of absorption of bile acids by the small gut after vagotomy. We presume that an increased volume of bile is expelled from the enlarged gall bladder, and as post-vagotomy bile contains a higher concentration of bile salts than before operation,⁷ the overall quantity of bile salts presented to the small gut is increased.

Lastly, Dr. Low-Beer suggests that because the ¹⁴C-glycocholate breathing test is normal diabetic diarrhoea is unlikely to be due to increased entry of bile salts into the colon. This test is based on the bacterial deconjugation of ¹⁴C-glycine from cholic acid, the glycine-¹⁴C being converted to carbon dioxide by bacterial and/or tissue enzymes. The test may be positive in bacterial overgrowth syndromes or if the enterohepatic circulation of bile salts is interrupted by ileal disease or resection, when both colonic and small-gut organisms may be involved. A

positive result depends, among other things, on the presence of appropriate bacteria for a period of time long enough to allow the above process to occur. Fromm *et al.*⁸ recorded four negative results in patients with ileal resection who had defective intestinal absorption of bile salts and they concluded that a negative result is likely to exclude bacterial proliferation in the small gut.

An alternative suggestion is that Dr. Low-Beer's negative results exclude "bacterial proliferation," particularly as no ileal disease has been demonstrated in diabetic diarrhoea. Bile acids, both conjugated and deconjugated, induce rapid emptying of the colon. This may not only reduce the time allowed for colonic organisms to split glycocholate but might also result in a decrease in the number of organisms in the large bowel.

We await with interest the results of direct measurement of faecal bile acids in patients with diabetic diarrhoea.—We are, etc.,

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Limitations of Laparoscopy in Diagnosis of Gonococcal Salpingitis

SIR,—We have both recently treated patients with gonococcal salpingitis in whom diagnosis was missed at laparoscopy. Both were women in their late teens who presented as emergencies with pelvic pain.

In the first case, there was slight pyrexia, some tenderness in the right iliac fossa, and on vaginal examination some right adnexal tenderness. Preliminary laparoscopy showed a normal uterus, normal ovaries, and normal fallopian tubes. As a good view of the appendix was not obtained laparotomy was performed. The appendix, which looked quite normal, was removed. The fallopian tubes looked normal but gentle massage produced a bead of pus at the fimbriae, a swab from which grew gonococci. In the second case the sequence of events was almost identical except that there was no pyrexia.

We would conclude that gonococcal salpingitis cannot be excluded with certainty by inspection of the serosal surface of the fallopian tubes at laparoscopy and wonder how many patients are being sent home the day after laparoscopy with the assurance that serious pelvic disease has been excluded. We also wonder how many normal appendices are removed by general surgeons when the diagnosis was in fact early gonococcal salpingitis.—We are, etc.,

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