ing in most patients with severe or mild proteinuria (Sharma *et al.*, 1971; Mahurkar *et al.*, 1973) and also when some of the haemodynamic effects of standing were simulated by the application of venous tourniquets to the thighs in the supine position (Gandhi *et al.*, 1971). Our present results are in line with the findings in these studies though at variance with those of others (Robinson *et al.*, 1964; Relman *et al.*, 1971; Rennie, 1971). We found that protein excretion decreased on standing upright, with a corresponding fall in creatinine clearance, in 80% of people. The remaining 20% were mostly younger persons in whom an increase in protein excretion was dissociated from changes in creatinine clearance.

Our study emphasizes the pre-eminence of glomerular filtration in regulating protein excretion in most normal people, since the fall in protein excretion results from a reduced filtered load. But a different mechanism must govern the increase in protein excretion when glomerular filtration falls. A partial failure of renal tubular reabsorption of filtered proteins has been postulated in exercise proteinuria (Poortmans, 1972; Pollak *et al.*, 1974) but has not been looked at in studies on posture. Increased glomerular permeability to protein from raised venous pressure has been suggested as the cause of orthostatic proteinuria (Bull, 1948/49), and this may also be the case in subjects whose protein excretion increases on standing but remains within normal limits.

Orthostatic proteinuria has been defined broadly as "a laboratory syndrome whose diagnosis requires the absence of qualitative proteinuria during recumbency and its presence during quiet ambulation or standing" (Robinson, 1970). On those criteria orthostatic proteinuria has been encountered in 5-20% of people (Robinson, 1964; Hamburger, 1968), but this finding may reflect the practice of estimating protein in the urine qualitatively and with variable fluid intake. Under these conditions the urine may be concentrated and the protein apparently raised on standing. In our study, in which fluid intake and the period of observation were the same in all people studied, the incidence of true orthostatic proteinuria was around 3%. Nevertheless, we found a much larger group (20%) in whom protein excretion increased on standing but remained within normal limits. This phenomenon, like orthostatic proteinuria, was commoner in younger people. Conceivably it may differ from true orthostatic proteinuria only quantitatively and may reflect the existence of a wider distribution curve for protein excretion when standing

We thank Mr. J. Becktal and Dr. A. Johnson, statisticians of Hines-VA Cooperative Studies Program Research Center, Hines, Illinois, for their help with statistical analysis.

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Serum α - Fetoprotein Levels in Patients with Cystic Fibrosis and their Parents and Siblings

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British Medical Journal, 1975, 1, 714-716

Summary

Patients with cystic fibrosis (C.F.) showed raised serum levels of α-fetoprotein (AFP). A moderate but significant increase in serum AFP was present in their parents and some siblings. There was no correlation between the clinical severity of the disease and serum AFP concentration. Samples from control groups with gluten-induced malabsorption and bronchiectasis had normal levels. Persistent synthesis of AFP may be an associated marker of C.F. genes, and estimation of serum AFP might help in detecting heterozygote carriers in families at risk.

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Introduction

Cystic fibrosis (C.F.) is the commonest lethal genetic disease in white Caucasians, occuring in about 1 in 2000 live births (Danks *et al.*, 1965; Brunecky, 1972). The gene frequency is estimated to be 2-5%. Obviously the mutation rate must be high or some heterozygote advantage must exist to keep the gene frequency at such a high level. In other ethnic groups C.F. is relatively rare (Wright and Morton, 1968). The inheritance is on a simple Mendelian autosomal recessive pattern but the possibility of more than one mutant allele has been suggested (Danes and Bearn, 1969). The main difficulty of providing adequate genetic counselling to relatives of children with C.F. other than the parents, who must be obligate heterozygotes of C.F. genes, is the failure in identifying with certainty asymptomatic carriers.

In C.F. the cell membrane metabolism and ion transport across it are abnormal, which might explain the changes in electrolyte content of sweat and other secretions. Glycoproteins in the membrane and secretions are suspected to be abnormal in chemical structure and charge. Lungs, pancreas, and liver are affected, and frequent pulmonary infections, especially with pseudomonas, are the main cause of morbidity and mortality. The multisystem involvement, which includes gut-associated organs, suggests a failure of optimal embryonic development which may be associated with persistent production of proteins

that are present in the fetus but are not detectable in adults.

We found significantly raised serum α-fetoprotein (AFP) concentrations in 18 children with C.F., their parents, and some of the siblings. Raised serum AFP levels may be valuable in detecting the heterozygote carriers of C.F. genes in families at risk.

Patients and Methods

Serum AFP was detected by Ouchterlony's agarose gel diffusion method and measured by counterimmunoelectrophoresis using a monospecific rabbit antiserum and standards containing known concentrations of AFP (Behringwerke). Samples below the limit of sensitivity of these methods were estimated by radioimmunoassay.

Six groups were studied. Serum samples were obtained from 18 children with C.F., 16 of their parents, and 14 of their siblings. C.F. was diagnosed by a sweat chloride higher than 60 mmol/l on pilocarpine ionotophoresis. In addition 22 healthy children matched for age and sex with C.F. patients, seven children with coeliac disease, and seven patients with bronchiectasis were investigated. All subjects except one 10-month-old infant with C.F. were over 1 year of age.

Results

The results are shown in the table. The serum AFP concentration in each of the 18 patients with C.F. was abnormally high. All the parents except one had a moderate serum AFP. The values in siblings showed a wide scatter and there seemed to be two subpopulations in this group: in seven there was a moderate rise (75-400 μg/l) comparable with that in the parents, whereas in the others the serum AFP level was within the range for healthy children. In samples positive by Ouchterlony's method there was a reaction of complete identity between AFP in the sera of patients with C.F. and that of their parents and siblings, cord blood, and a sample from a patient with hepatoma.

Serum α-Fetoprotein Concentrations (μg/l) in Groups Studied

	No. of Subjects	Range	Log Mean ± S.E. of Mean
Healthy controls	22	5–25	10 ± 0·11
Children with C.F.	18	56–8825	690 ± 1·18
Parents of children with C.F.	16	25–568	178 ± 0·85
Siblings of children with C.F.	14	6–400	43 ± 1·60
Patients with coeliac disease	7	7–25	12 ± 0·12
Patients with bronchiectasis	7	4–20	9 ± 0·12

There was no correlation between the serum AFP level and the severity or nature of clinical manifestations. None of the patients or their parents and siblings showed any evidence of liver cell dysfunction.

All the patients with coeliac disease and bronchiectasis had serum AFP concentrations well within the range for healthy controls.

Discussion

AFP is synthesized mainly by the liver and is a major component of fetal serum. In man the peak synthetic activity occurs around the 13th week of gestation, when a concentration of 3-4 g/l is achieved. The level decreases progressively until it is about 30 mg/l at birth (Gitlin and Boesman, 1966; Chandra 1974). The evolution of sensitive detection methods has shown the presence of AFP in small amounts in the sera of healthy adults (Ruoslahti and Seppala, 1971). In postnatal life a raised serum AFP concentration has a diagnostic significance in hepatoma (Abelev, 1971; Masopust *et al.*, 1971), malignant teratoma (Abelev, 1971), neural tube defects (Leek *et al.*, 1973; Brock *et al.*, 1973), neonatal hepatitis (Chandra, 1973, 1975), and Indian childhood cirrhosis (Nayak *et al.*, 1972; Chandra 1974, 1975). Raised serum AFP levels are reported in ataxia telangiectasia (Waldman and McIntire, 1972). In the amniotic fluid AFP concentrations higher than 60 mg/l are associated with impending or actual death, anencephaly, and spina bifida (Brock and Sutcliffe, 1972; Allan *et al.*, 1973).

We observed raised levels of AFP in the sera of C.F. patients as well as their parents who are obligate heterozygotes for the abnormal genes. Continued AFP synthesis may be an associated marker of, among other conditions, the C.F. genes. If so, this would make possible the detection of asymptomatic heterozygotes in families at risk. Earlier attempts in this direction have been largely unsuccessful. The serum of children with C.F. and their parents contains a ciliary dyskinetic factor for rabbit tracheal explants (Spock *et al.*, 1967), fresh water mussels (Besley *et al.*, 1969), and oysters (Lockhart *et al.*, 1968). The utility of this factor as a genetic marker is very doubtful, however, since the test is cumbersome and lacks universal reproducibility and reliability (Cherry *et al.*, 1971). Also cilia-inhibiting activity may be observed in some fractions of normal serum as well. The increased metachromasia seen in fibroblasts cultured from C.F. homozygotes and heterozygotes (Danes and Bearn, 1968) raised the interesting possibility of valuable antenatal diagnosis. Technical difficulties, failure to reproduce the results, and the considerable overlap between findings in affected and healthy subjects and in the same cell line at different times, however, make this test unreliable. Recent evidence suggests that RNA methylation in short-term lymphocyte cultures is reduced in C.F. homozygotes as well as heterozygotes (Rennert *et al.*, 1972).

Among siblings of C.F. patients we found a bimodal distribution of serum AFP levels with either normal or raised values. The children with a moderate rise in serum AFP concentration probably represent the heterozygote carriers of C.F. as their values were comparable with the findings in the parents, who must be obligate heterozygotes. In autosomal recessive traits the proportion of carriers to normal subjects in a sibship should theoretically be 2 : 1, whereas this ratio was 1 : 1 in our study. We considered relatively small numbers for genealogical analysis, however, and further studies are clearly indicated to confirm and extend these observations.

The cause(s) and mechanism(s) of continued or renewed AFP synthesis in postnatal life are poorly understood. A failure in the development and maturation of gut-associated tissues, especially the liver, may be accompanied by the production of embryonic proteins long after these are normally switched off. In C.F. the pathogenesis of liver involvement is not clear. Possibly normal maturation processes during fetal life are adversely affected by C.F. genes, leading to the persistence of embryonic cell lines capable lo AFP synthesis and at the same time making the liver more susceptible to damage such as fibrosis, cholestasis, and multilobular cirrhosis.

We suggest that serum AFP concentrations should be determined in all first-degree relatives of patients with C.F. Raised AFP levels are associated with the presence of C.F. genes, and if other known causes of persistent synthesis of AFP can be excluded it would help in the detection of C.F. heterozygote carriers and thereby in genetic counselling.

We thank Mrs. Anna Kennedy for help in organizing the cystic fibrosis clinic and Miss Patricia Taylor for technical help.

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Highly Selective Vagotomy for Duodenal Ulcer : Do Hypersecretors Need Antrectomy?

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British Medical Journal, 1975, **1**, 716-718

Summary

Two to five years after highly selective vagotomy (H.S.V.) for duodenal ulcer the results were similar in patients with high preoperative maximal acid outputs and those with lower acid outputs. Pain of ulcer type was experienced at some time by 6% of patients from each group, but it was mild and transient in some. No patients had recurrent ulceration at endoscopy or laparotomy, while incidence of individual symptoms was about equal in the two groups.

Hence H.S.V. is adequate surgical treatment for patients with both duodenal ulceration and high levels of acid secretion. Antrectomy in such patients is not necessary provided that the incidence of incomplete vagotomy can be kept low.

Introduction

Some authorities customarily add an antrectomy to vagotomy when operating for duodenal ulcer (Herrington, 1969; Smithwick *et al.*, 1961). Others are more selective and base their choice of operation on the magnitude of preoperative acid output (Bruce *et al.*, 1959; Small *et al.*, 1967). Vagotomy with antrectomy for patients who have a very high maximal acid output before operation and vagotomy with a drainage procedure for the remainder has been strongly advocated by Kronborg (1972, 1974) and Robbs *et al.* (1973). Antrectomy with vagotomy undoubtedly diminishes the risk of recurrent ulceration, but operative mortality is increased; side effects occur more often than after the newer types of vagotomy (Amdrup *et al.*, 1974); and long-term weight loss is greater (Goligher *et al.*, 1968).

Our purpose was to find out whether highly selective vagotomy (H.S.V.) provided adequate surgical treatment for all patients with duodenal ulcer or whether antrectomy was also needed in the hypersecretors. Since 1969 we have treated all patients having surgery for duodenal ulcer, irrespective of their preoperative maximal acid output by H.S.V. without drainage (Johnston and Wilkinson, 1969, 1970; Amdrup *et al.*, 1974). This is an even more conservative operation than truncal or selective vagotomy with drainage because it leaves the gastric antrum vagally innervated and the pyloric sphincter intact. Patients were reviewed at a gastric follow-up clinic at yearly intervals to find out whether those who had had hypersecretion of acid before operation had worse clinical results or a higher incidence of recurrent ulceration than patients whose maximal acid output had been normal.

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Methods

Patients.—As the women's results did not differ from the men's they were considered together. Only patients who had undergone elective H.S.V. in the treatment of chronic duodenal ulcer two to six years previously were included. The maximal acid output in response to pentagastrin had been measured in each patient both before operation and five to 10 days after vagotomy. Each patient had also undergone an insulin test five to 10 days after operation. Patients were followed up at yearly intervals at a gastric follow-up clinic. They were interviewed by a panel of doctors who did not learn the patient's diagnosis or the nature of the operation until they had assessed the answers to standard questions and made their collective verdict according to a modified Visick system of grading (Goligher *et al.*, 1968).

Criteria of Hypersecretion.—Peak acid output as assessed by the pentagastrin test (P.A.O.) was calculated as the highest of four consecutive five-minute readings multiplied by three and expressed as mmol (mEq) HCl/hour. The titration end-point was pH 7. Hypersecretion was defined arbitrarily as a P.A.O. greater than 50 mmol/h in men and 40 mmol/h in women: firstly, because few normal people are found in our laboratory to secrete more acid than this; and, secondly, because of Kronborg's findings (1974). He found recurrent ulceration after truncal vagotomy and drainage in 21% of men whose preoperative P.A.O. was greater than 46 mmol/h and in 28% of women whose P.A.O. was greater than 42 mmol/h before operation. According to our criteria 40 patients were hypersecretors. The clinical results in these patients were compared with those in 60 patients who had "normal" acid secretion, which was defined as a P.A.O. of 30-50 mmol/h in men and 25-40 mmol/h in women. We had intended to include a third group of "hyposecretors" with P.A.O. less than 30 mmol/h in men and 25 mmol/h in women, but the numbers were so small that analysis of the clinical results seemed pointless.

TESTS OF ACID SECRETION

Pentagastrin Test.—The dose of pentagastrin was 6 μg/kg body weight intramuscularly before operation and 10 μg/kg intramuscularly after H.S.V. (Johnston and Jepson, 1967; Johnston *et al.*, 1973 a).

Insulin Test.—Basal acid output was collected for one hour. Soluble insulin 2 U/kg was then injected intravenously and acid output collected for a further two hours (Johnston *et al.*, 1973 b). Blood-glucose determinations, on venous blood samples collected 30 and 45 minutes after the injection of insulin, confirmed that glucose