We agree with Dr Gregg that comparison with normal values may be misleading. Clearly, predicted values must be established for individual patients by their doctor.

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Genetics and lung disease

SIR,—Dr Julian Hopkin recently wrote about the important relations between lung disease and several common genetic disorders.[1] For the sake of completeness some further comments on deficiency of α_1 antitrypsin are needed, and I would draw attention to studies carried out by the British Thoracic Society.[2,3]

In subjects homozygous for the Z phenotype the serum α_1 antitrypsin concentration is 10-20% of the normal value; at this low concentration severe emphysema can occur even in those who have never smoked, and there is no doubt that smoking has a considerable adverse effect on the prognosis.[2] In subjects heterozygous for type SZ the serum α_1 antitrypsin concentration is 30-40% of the normal value; in subjects with this phenotype (in contrast to type ZZ) emphysema occurs only in smokers[3] and the age at onset and the radiological features of the disease are similar to those in patients with emphysema with a normal serum α_1 antitrypsin concentration. The SZ phenotype on this evidence in itself carries little or no extra risk of emphysema. There seems to be a safe threshold at 20-30% of the normal serum α_1 antitrypsin concentration, implying that replacement treatment should logically be reserved for those with type ZZ.

Dr Hopkin also mentions the possibility of antenatal diagnosis, but this is relevant only in the context of neonatal hepatitis, which occurs, for unknown reasons, in 10-20% of newborn infants with type ZZ. In practice, antenatal diagnosis is mainly used for screening a subsequent pregnancy in a couple who have already had a child with type ZZ with severe hepatitis or cirrhosis and are prepared to accept termination rather than risk a similar occurrence.[4]

A booklet about the condition for the guidance of patients has been sponsored by the Chest, Heart and Stroke Association and is available on request.

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Diagnosing pancreatic masses

SIR,—Mr M R Zeiderman and colleagues' article on diagnostic difficulties in patients with a pancreatic mass[1] failed to mention the important role of endoscopic retrograde cholangiopancreatography in the diagnosis and treatment of extrahepatic biliary obstruction. Not only can this method give excellent views of the biliary and pancreatic ductal systems but it also enables immediate biopsy and treatment by sphincterotomy or endoscopic insertion of a biliary stent across the stenosis.[2]

In two of the cases described in the article the patients underwent both percutaneous transhepatic cholangiography and insertion of an internal biliary endoprosthesis (Carey-Coons). In expert hands endoscopic retrograde cholangiopancreatography can give views of the pancreatic duct (not seen on percutaneous transhepatic cholangiography) as well as the biliary tract and of any obstructing ampullary lesion. Tissue for diagnosis can be obtained with forceps or by brush biopsy, aspiration of pancreatic juice, or direct transduodenal needle aspiration. Drains and stents can be passed across the stenosis during the procedure, thus reducing the procedures the patient has to undergo.

Cytological examination of tissue is important before treatment in all cancers, and the role of endoscopic or percutaneous aspiration should be emphasised. Outpatient diagnosis of breast cancer is an excellent example,[3] although it does require a skilled cytologist.

In summary, investigation of a jaundiced patient with a mass at the lower end of the bile duct should include endoscopic retrograde cholangiopancreatography for radiological confirmation, direct visualisation, tissue diagnosis, and potential palliation of this distressing condition, which will reduce the number of invasive and potentially distressing investigations.

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Daughters of stilboestrol

SIR,—As Dr Mary Wingfield says in her editorial, most of the women who were exposed to stilboestrol in utero are now in the reproductive phase of their lives.[1] The true relation between exposure to stilboestrol in utero and infertility has not been studied in a controlled manner,[2] but, from our review of published reports and our own experience, we believe that the effects of stilboestrol on fertility are related less to the anatomical changes it may induce and more to the effects of the treatment of these changes. Three patients in their early to mid-30s who had been exposed to the drug in utero and attended our reproductive medicine clinic or in vitro fertilisation service illustrate this.

Two of the women had had cautery to the ectocervix because of either excessive vaginal discharge or cervical dysplasia eight and 10 years before presentation, resulting in cervical stenosis and deficient production of cervical mucus. One of these two had three attempts at assisted conception, none of which were successful. The first procedure was in vitro fertilisation, at which transcervical embryo transfer was achieved only under general anaesthesia, and the two others were gamete intrafallopian transfer procedures, which were technically satisfactory but unsuccessful. The other patient with cervical stenosis had a single attempt at gamete intrafallopian transfer; this was successful, and she is now in the second trimester of a singleton pregnancy. The third patient was unaware that she had been exposed to stilboestrol until she was referred because of an abnormal cervical appearance and smear test result. At examination under anaesthesia she was found to have a cervical hood, which was excised, but the result of colposcopic examination was normal. She conceived naturally and is now in the second trimester of the pregnancy. Her uterus and cervix were hypoplastic, and investigations of her fertility yielded normal results.

The evidence from these patients suggests that there is no obvious difficulty in maintaining a pregnancy once it is established; pregnancy can be achieved naturally or by assisted conception. This concurs with the experience of others relating to both fecundity[3] and the response to in vitro fertilisation.[4] We agree with Dr Wingfield that caution is required with regard to cervical surgery in patients who have been exposed to stilboestrol. Clearly, definitive treatment is necessary for cervical intraepithelial neoplasia, but if unfamiliar appearances are present or leucorrhoea is the main complaint overzealous treatment should be avoided. Even in normal women cervical surgery or biopsy may lead to inadequate production of cervical mucus and reduced fertility.[5] In women who have been exposed to stilboestrol and have a hypoplastic cervix the effects of surgery are potentially more serious: as Dr Wingfield points out, the incidence of cervical stenosis in these patients when treated for cervical intraepithelial neoplasia is 75%.[6]

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Creutzfeldt-Jakob disease and blood transfusion

SIR,—We wish to clarify certain statements made by Mr Alan M Watkins in his letter on Creutzfeldt-Jakob disease and blood transfusion.[1]

On 30 December 1985 Professor R D G Milner, chairman of the Health Services Human Growth Hormone Committee, sent a letter to the director of this centre. We assume that a similar letter was sent to all other directors of regional transfusion centres. This letter stated that there were reports of four patients who had died of Creutzfeldt-Jakob disease who had previously been treated with human growth hormone. One of the cases had occurred in the United Kingdom. The letter stated that at its meeting on 9 December 1985 the Health Services Human Growth Hormone Committee had recommended that Professor Milner should write to directors of regional transfusion centres to request that "patients who had been treated with growth hormone be excluded as potential blood donors."

We accordingly took action and on 23 January 1986 issued an instruction to our medical officers that "any donor who has been treated with human growth hormone cannot be accepted as a blood donor, because of the *very remote* risk of transmission of Creutzfeldt-Jakob disease." This instruction was incorporated into our manual of standard procedures at that time.

In 1989 the Department of Health asked the blood transfusion service to include a specific reference to human growth hormone in the docu-