were enlarged and infiltrated. The urogenital, endocrine, reticuloendothelial, and central nervous system were macroscopically normal. In the chest there were bilateral small straw-coloured pleural effusions. Both lungs were rather voluminous but firm, with a granular appearance and texture.

Histological examination of the formalin-inflated lungs revealed diffuse and focal interstitial fibrosis. Haematoxylin-van Gieson staining showed collagen in considerably increased amounts in the interstitium, with occasional areas showing even greater collagen deposition. Intra-alveolar fibrosis, as seen in organisation of proteinaceous exudates, was not evident. Some oedema was also seen. Occasional foci of plump expanded cells, probably of alveolar origin, were present, projecting into alveolar lumina. There was no evidence of *Pneumocystis* or fungi. A single very small focus of secondary adenocarcinoma was identified in one of numerous sections examined.

These findings confirm that this patient had interstitial fibrosis. As other aetiological factors have been excluded, we feel that the interstitial fibrosis developed as a result of therapy with 5-fluorouracil and mitomycin C.

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Practical problems with the Clinitest

SIR,—Recent reports in the *BMJ* (31 March, p 859) and elsewhere^{1,2} have highlighted the potential hazard to the management and control of diabetes in patients with congenital colour vision defects who use the Ames Clinitest. With congenital colour vision defects in 8% of the male population this represents a hazard to one in 12 male diabetics. Since diabetics are known to have acquired colour vision defects associated with their diabetes,³ we recently conducted a study⁴ aimed at determining how well diabetic patients in general coped with colour matching on the Clinitest. The study, conducted during May of this year, produced some surprising findings.

Although diabetics were found to make significantly more errors on the test than a control group with normal colour vision (the diabetics systematically overestimated their sugar concentration for concentration levels $\frac{1}{4}$ %, $\frac{1}{2}$ %, $\frac{3}{4}$ %, 1%), the control group also made errors in the same direction on the test. In particular, diabetics presented with a nominal $\frac{1}{2}$ % concentration of dextrose solution matched on average $1\frac{1}{2}$ Clinitest steps further towards the red (that is, indicating a higher sugar concentration). Furthermore, 14 out of 36 diabetic matches were in error by two Clinitest steps, so that a prepared solution of $\frac{1}{2}$ % sugar concentration (actually measured at 0.49%) was read as a 1% concentration. The control group of normal subjects, however, matched the same $\frac{1}{2}$ % solution on average at the $\frac{3}{4}$ % concentration level. So while the diabetic matches were one and two Clinitest steps away from the expected nominal test match, they were only up to one step further in error than the match achieved from subjects with normal colour vision. These matching errors, which were all of overestimation, occurred for prepared solutions in which the

measured dextrose concentrations were always marginally less than the nominal figure. The errors in matching were comparable whether made under typical domestic tungsten lighting (CIE illuminant A) or artificial daylight (CIE illuminant C).

Analysis by reflectance spectrophotometry of the prepared solutions and coloured reference papers showed that the solutions were indeed slightly redder than their nominal paper reference colours, thus substantiating the "errors" made by the control group of subjects with normal colour vision. Furthermore, for each concentration the solution-paper colour combination had characteristically different spectral reflectance curves (that is, were metameric), indicating that the matches are particularly vulnerable not only to changes in the type of illuminant being used but more importantly to changes in an observer's colour vision mechanisms.

We draw attention to these findings and ask whether their clinical implication for diabetic control is sufficient to warrant a thorough re-evaluation of the test.

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¹ Taylor, W O G, *Transactions of the Ophthalmological Society of the United Kingdom*, 1972, **92**, 95.

² Thompson, D G, Howarth, F, and Levy, I, *Lancet*, 1978, **1**, 44.

³ Lakowski, R, Aspinall, P, and Kinnear, P, *Ophthalmic Research*, 1972, **4**, 145.

⁴ Aspinall, P, Hill, A R, and Cameron, D, in *Proceedings of Fifth Symposium of the International Research Group on Colour Vision Deficiencies*, London, 1979 (in press).

The grumbling appendix

SIR,—It is interesting that this myth should still need a leading article (4 August, p 294)—interesting also that your recent references mostly come from America. In Britain the incentives for retaining the diagnosis "chronic appendicitis" are nowadays seldom tangible, but they are nevertheless difficult to resist. For, however stringent the chief may be in eliminating lily-white appendicectomies he is up against the enthusiasm of young men keen on surgery, and of young patients and parents who are even keener on surgery. We can all remember our early days, when such an alliance enabled us to get our appendicectomy time down to single figures! So let us not be too hard on these young men who make the most of their opportunities, or indeed on the young patients for making full use of a syndrome which has solved many a conflict for them.

But what are we to tell the anxious parents? Firstly, we must say, there is no present evidence of disease, acute or chronic, in the appendix. Secondly, the child may nevertheless develop an acute appendix at some time, like anyone else. Thirdly, they will ask "What, then, is the trouble?" and it is no use saying, "There is nothing wrong." Patients and parents will be reassured if we offer a reasonable physical explanation; for these cases I found one very acceptable (and frequently true) label: "Inflamed internal glands—he'll grow out of it."

There is one point which will help in trying to sort out the rare genuine interval case from the spurious: the pain of onset in acute

appendicitis is typically in the mid-epigastrium, not at the umbilicus. But don't let our patients get to know this.

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Doctors and children's teeth

SIR,—With reference to the letter by Professor P J Holloway (11 August, p 390) on the subject of fluoride tablet dosage, we have been using the dosage (up to 2 years 0.5 mg/day, 2-10 years 1 mg/day) first recommended in your columns¹ and no adverse reaction report (yellow card) has been sent to the DHSS in respect of dental fluorosis.

Higher dosages are commonly used in Australia and have not led to complaints from either dentists or members of the public. Only one paper dealing with dosage has been published in the *British Dental Journal* in recent years.² This actually suggested a higher dosage, 0.75 mg, for the ages of 16-24 months while reducing the dosage in the first eight months to 0.25 mg. Since Professor Holloway admits that greater protection is given by the larger dose we are prepared to take the very remote risk of a claim from a member of the public for causing fluorosis in view of the fact that our sales average 40 million tablets a year.

It is not irrelevant to remark that tablets of 0.25 mg, while available at many dentists, are not in general stocked by pharmacies.

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¹ *British Medical Journal*, 1956, **1**, 1312.

² Geddes, D A M, Jenkins, G N, and Stephen, K W, *British Dental Journal*, 1973, **134**, 426.

Disposable insulin syringes

SIR,—Dr Arnold Bloom and colleagues (2 June, p 1467) report the satisfactory use of "disposable" insulin syringes on more than one occasion. The availability of modern syringes is also of assistance in relation to the precision of administering insulin. The British Standard insulin syringes, with a Luer needle, have a "dead space" of about 0.05 ml, which contains 4 units of 80 U/ml insulin. Thus, if one mixes two insulin types into a single syringe, there can be considerable inaccuracy, particularly if one of the doses of insulin is small. In addition, the large dead space also causes an unnecessarily large air bubble in the syringe on drawing up insulin, and patients have to be instructed in the techniques of injecting the bubble back into the insulin bottle. When the syringe is washed after use insulin to the value of 1.5p may be discarded.

We have recently undertaken a clinical trial of 1-ml disposable syringes (Becton-Dickinson, sterile-fluid-path, Plastipak syringes) in 17 children and 22 adult insulin-dependent diabetics. Instead of the usual 20 marks/ml, the syringes were compatibly marked with 80 marks/ml for use with only 80 U/ml insulin. The dead space of about 0.01 ml meant that the air bubble on drawing up the insulin was small enough to be ignored. Twenty-two patients had an insulin dose less than 10 U, but none had difficulty in measuring the small doses, the syringes being marked at 2-unit intervals. One of the fears relating to the

introduction of 100 U/ml insulin is difficult in measuring small doses, but this does not seem to be a problem with modern disposable syringes, even though it might be with the current British Standard glass syringe.

Twenty (51%) patients had previously used the 20 mark/ml scale and preferred the new scale with direct-reading 80 marks or units/ml; 28 (72%) thought that errors of doses were less likely with the syringes with the new scale; 35 (90%) preferred the disposable syringes to the glass syringes, while two found them equally convenient and two found them inferior. Twenty-six (67%) said they would be willing to pay 5p per syringe for the convenience of using it, whereas only 23% said they would be willing to pay 10p per syringe.

This study supports the advantage of changing to disposable syringes. A surprising number of patients would appear to be willing to purchase a well-designed disposable syringe-needle combination in preference to current glass syringes. With regard to multiple use of disposable syringes, crystalline insulins occasionally block the needle and prevent reuse. Several of our patients have commented that the needles become considerably less sharp after three or four uses. Even with that amount of reuse, it would probably be advantageous for the DHSS to supply disposable syringes rather than the current glass syringes, particularly if one takes into account the cost of insulin discarded on washing the glass syringes.

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Lupus-like autoimmune syndrome after levodopa and benserazide

SIR,—We refer to the paper of Dr Robert M Bernstein (2 June, p 1461) reporting a case of levodopa-induced autoimmune reversible haemolytic anemia and to the paper of Dr Julien Bensaid and others (16 June, p 1603) reporting a case of pindolol-induced systemic lupus erythematosus. We have seen a patient who developed a lupus-like autoimmune syndrome during treatment with a product containing levodopa and benserazide, a known carboxylase inhibitor.

A 62-year-old man with sclerotic heart disease was prescribed levodopa 600 mg daily plus benserazide 150 mg daily for Parkinson's disease in July 1976. About two months after starting this treatment—which completely cleared the neurological symptoms—he presented with weakness, anorexia, diffuse joint pains, fever, "butterfly" erythema, erythema on the back, lumbosacral region, and anterior surface of the thighs, hepatomegaly, and malleolar oedema.

Blood tests showed: haemoglobin 13.5 g/dl; red blood count $4.1 \times 10^{12}/l$; white cell count $5.9 \times 10^9/l$, neutrophils 53%, eosinophils 9%, lymphocytes 33%, monocytes 4%; platelets $130 \times 10^9/l$; total bilirubin 17.8 $\mu\text{mol/l}$ (1.04 mg/100 ml), serum aspartate transaminase 240 U/l; alanine transaminase 240 U/l; total proteins 63 g/l, albumin 39.4%, globulins: α_1 3.3%, α_2 10.3%, β 17%, γ 30%; bromsulphthalein retention 27% after 45 minutes. Urinary investigations showed protein 5 g/l, microhaematuria, hyaline granular casts, and creatinine clearance 65 ml/min. Hepatitis B

surface antigen was absent and C3 concentration was 600 mg/l. The RA test titre was 1/360 and the Rose Waaler titre 1/640, and LE cells were absent. Tests for antibodies showed: antinuclear antibodies 1/260; perinuclear antibodies + — —; anti-smooth muscle antibodies + + +, anti-native DNA antibodies absent. Lymphocyte cultures with levodopa and benserazide were negative.

Withdrawal of treatment caused the subjective symptoms and fever to disappear. Sixty days later the erythema was no longer visible and the serological indices had returned to normal except for: globulin 26%; Rose Waaler titre 1/80; bromsulphthalein retention after 45 minutes 12%; and anti-smooth muscle antibodies + — —.

Other authors¹⁻⁴ who have reported levodopa-induced autoimmune syndromes noted the symptoms only many months after the start of treatment (not less than eight months) and with doses of 2 to 4 g daily; in addition, none observed rapid spontaneous disappearance of the autoantibodies. We have found no other report of a levodopa-induced SLE-like syndrome; Chrusciel⁵ cited a lupus-like syndrome in rats treated with 50 mg/kg/day for at least nine weeks with benserazide, but no case has been reported in man. While the rapid onset of lupus-like syndrome at low doses of levodopa suggests the triggering of latent SLE, the nearly complete remission after stopping the drugs points to an autoimmune origin. It may be that, as other authors have suggested, levodopa has an adverse effect on nucleoproteins or on nuclear fragments, with the release of autoantigens, probably as is the case with the isomer α -methyldopa. This hypothesis might be confirmed by the negative results of lymphocyte stimulation tests, which exclude a direct action on the T lymphocytes. It seems most unlikely that benserazide in such small doses could have caused such a rapid onset of an immune syndrome.

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¹ Lindström, F D, Lieden, G, and Endström, M S, *Annals of Internal Medicine*, 1977, **86**, 298.

² Cotsias, G C, and Papavasiliou, P S, *Journal of the American Medical Association*, 1969, **207**, 1353.

³ Territo, M C, Peters, R W, and Tanaka, K R, *Journal of the American Medical Association*, 1973, **226**, 1347.

⁴ Wanamaker, W M, et al, *Journal of the American Medical Association*, 1976, **235**, 2217.

⁵ Chrusciel, M, *European Journal of Pharmacology*, 1969, **8**, 192.

Smoking and anaesthetics

SIR,—In the last sentence of their paper (11 August, p 355) on smoking in pregnant women, Dr Judith M Davies and others raised the question of anaesthesia in smokers once again. While agreeing that abstinence from smoking should be encouraged before anaesthesia, there are problems which must be faced. It is usually impossible to admit patients earlier than 48 hours before anaesthesia, and in most cases the doctor cannot devote enough time to persuading patients to stop smoking earlier than this. If a heavy smoker, with a very high consumption of cigarettes, who also has chronic bronchitis stops smoking the chest tightens up for the next 48 hours, and it becomes impossible to expel tenacious sputum.

This gradually relieves itself, but during this period the patient is miserable and is coughing constantly and without relief.

I therefore suggest that either smoking should cease four weeks before operation or it should be allowed to continue with due regard to premedication, night sedation, etc, up to the morning of the operation. Incidentally, if one discusses the difficulty of stopping smoking or drinking with a patient who is dependent, or has been dependent, on both, one is told that stopping smoking is more difficult, mainly because it is socially acceptable at any hour of the day or night.

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Fetal malnutrition—the price of upright posture?

SIR,—In his excellent and stimulating article Dr André Briend (4 August, p 317) reminds us that in most population studies the mean birth weight is slightly lower than the optimal birth weight—that is, the birth weight associated with the lowest perinatal mortality. He then argues that this disproves the otherwise tenable hypothesis that slight fetal growth faltering occurring just before birth is an adaptive process to facilitate delivery.

Man's successful adaptation has always depended on his cerebral efficiency, and it may well be that in such terms a slight increase in perinatal mortality has proved a small price to pay if the smaller fetal heads of those who did survive contained less birth-damaged and more efficient brains.

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Yersinia arthritis

SIR,—We read with interest the papers by Dr D Y Bulgen and others and Drs J T Scott and N S Mair (12 May, pp 1250 and 1251) describing the arthritic sequelae which may follow infection with *Yersinia enterocolitica*. Pigs are the only source from which serotypes of *Y. enterocolitica* causing human disease have been regularly isolated and are therefore assumed to be the most likely reservoir for infection in man. In view of the apparent increase in infections caused by *Y. enterocolitica* and the lack of data regarding the incidence of this organism in British farm animals we have investigated the caecal contents of healthy pigs for the presence of *Y. enterocolitica*. Animals from farms in Hampshire, Surrey, and Sussex were slaughtered at a local abattoir and caecal contents from 169 pigs were collected immediately after evisceration.

Pooled samples of caecal material were examined by direct plating on to deoxycholate citrate agar containing 1% sucrose (DCLS) and a "cold-temperature enrichment" technique undertaken by inoculating about 1 g of pooled contents into 5 ml of 0.067M phosphate-buffered saline (PBS) at pH 7.6. The inoculated PBS was stored at 6°C for three weeks before plating on to DCLS agar. Plates were incubated at 30°C for 48 hours, after which at least three colonies resembling control strains of *Y. enterocolitica* were submitted to further investigations. Oxidase and urease activity, lactose fermentation, and phenylalanine deamination were determined on each isolate followed by further confirmatory biochemical tests on organisms giving reactions resembling *Y. enterocolitica* in the initial tests.

Caecal contents from 39 pigs were pooled in