control to our procedures. In particular, we should be able to define the indications and contraindications—both relative and absolute—for colonoscopy.

Dr Anderson and others do not state why colonoscopy was performed; presumably it was to investigate the suspected intraluminal mass seen on barium enema examination. Nor do they explain the disturbing statement that: "Barium was noted outwith the colon at the level of the iliac crest."

After the barium enema their toxic 71 year old woman had 48 hours of colonoscopy preparation followed by partial colonoscopic examination. Subsequently her condition deteriorated further with signs of intra-abdominal disease; at laparotomy a caecal volvulus was identified as well as a left paracolic abscess related to an area of known diverticular disease. Without the benefit of a critical analysis by the authors of the events leading up to surgery one must inevitably question the wisdom of having performed colonoscopy when there was any suspicion of bowel perforation, as "the presence of barium outwith the colon" strongly suggests. Patients with active inflammatory bowel disease or diverticular disease should not have rigorous bowel preparation before colonoscopy as this can exacerbate their condition, and the suspicion of perforation should be an absolute contraindication to both the procedure and its preparation.

Unless the authors can offer a satisfactory alternative explanation one must conclude that their patient had perforated an inflamed diverticulum before or at the time of her barium enema and that the bowel preparation and colonoscopy were contraindicated and potentially harmful. The issue of whether or not colonoscopy caused a caecal volvulus or accelerated one in evolution seems a secondary consideration. It is hard to escape the conclusion that this patient would have been better served by early laparotomy to look for a site of bowel perforation.

Complications of any endoscopic procedure inevitably occur more often in debilitated patients with appreciable bowel disease. Unless we are critical of our use of colonoscopy such patients will increasingly be exposed to unnecessary risks.

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****We sent a copy of this letter to the authors, who reply below.—ED, *BMJ*.

SIR,—We entirely agree with Dr Baillie that to maintain the safety record of colonoscopy patient selection is crucial. In the case described the reason for colonoscopy was to investigate the nature of the suspected intraluminal mass lesion and the reason for reporting the case was to describe a previously unreported complication.

The much abbreviated barium enema report was possibly misleading. The "barium noted outwith the colon" was in fact outside the lumen and thought to be within the wall of the colon. It was difficult to distinguish from a diverticulum. This fact, together with the favourable clinical response to treatment (antibiotics) and the patient's refusal to submit to surgery, suggested to us that the indications for colonoscopy outweighed the relative contraindications. At the time of endoscopy the patient had been without fever for more than a week after her barium enema, and the colon in the left iliac fossa, though palpable, was not tender.

After colonoscopy the patient's symptoms and signs were those of obstruction and subsequent strangulation, not of perforation. The relative contraindications were much in mind, and to exclude the possibility that a diverticulum might have perforated when no neoplastic lesion had been found plain abdominal radiographs were taken a few hours after the procedure. These and subsequent radiographs showed no free gas within the peritoneal cavity.

Emergency laparotomy was carried out 48 hours later because radiological and clinical examination of the abdomen showed evidence of caecal volvulus. At laparotomy, although a small, well walled off paracolic abscess was found in an area of colon severely affected by diverticular disease, this did not interfere with the subtotal colectomy, nor was it the cause of the patient's immediate preoperative symptoms and signs. Had the complication of volvulus not ensued the condition might have settled completely on conservative management.

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Screening for fetal malformations

SIR,—Dr R C M Cook and others (2 April, p 1149) suggest that rather than terminating some abnormal pregnancies we might consider delivery followed by appropriate treatment. How I wish we could persuade our patients to accept this advice.

As an obstetrician I have recently been concerned with two pregnancies where I attempted to pursue this course. The first couple were adamantly opposed to termination of pregnancy and refused screening for neural tube defects. They agreed, however, to a routine ultrasound scan for dating, and when this was done a large exomphalos was noted. I spent much time explaining to them the nature of this abnormality, and we obtained advice from the paediatric surgeons and the paediatricians about the prognosis, treatability, and possible curability of this condition. At the end of the day the parents decided they could not possibly continue with the pregnancy in the knowledge that the fetus was abnormal and, despite their strong feelings against abortion, they opted for a prostaglandin termination of pregnancy.

The second couple had had a diagnostic amniocentesis performed to investigate a raised serum α-fetoprotein concentration and, by coincidence, we found that the baby had Klinefelter's syndrome. We informed the parents of this condition, and after a lengthy explanation of its nature they opted for termination, mainly because they could not bear the thought of having a child with any type of abnormality and, in particular, they were upset by the idea that their child would be sterile.

It seems that when people are told that they have an abnormal baby many find it extremely difficult to accept the abnormality, whatever the nature or prognosis. I found it particularly interesting that the couple who were so adamantly opposed to abortion in principle found themselves only too willing to have a termination when it was their pregnancy that was affected, albeit with a condition that is sometimes eminently treatable.

It is only too easy to formulate one's ideas and ideals and to offer advice in letters to the journals; it is less easy to adhere to this advice when faced with patients to whom the condition in their baby is a reality and who are unwilling to accept the idea of an abnormal baby, whatever the type or degree of abnormality.

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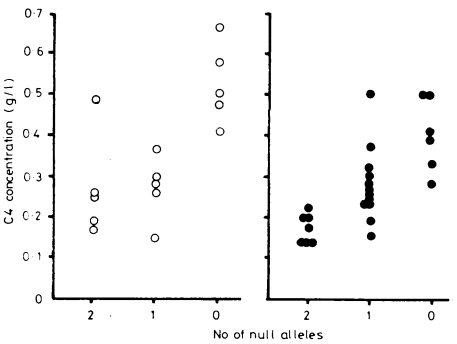
Low serum C4 concentrations in insulin dependent diabetes mellitus

SIR,—We agree with the suggestion of Dr D Vergani and others (19 March, p 926) that an inherited deficiency of the fourth component of complement (C4) is associated with insulin dependent diabetes mellitus. As we[1] and others[2] have shown previously, two of three high risk supratypes (HLA—B8 Bf*S C4A*Q0 C4B*1 DR3 and HLA—B18 Bf*F_1 C4A*3 C4B*Q0 DR3) contain null alleles at the C4 loci. Furthermore, we and others[3] have found that serum C4 concentration is related in general to the number of C4 null alleles, as shown in the figure.



Serum C4 concentrations versus number of C4 alleles in 15 patients with insulin dependent diabetes mellitus (left) and 25 healthy subjects (right). The number of null alleles was assigned after C4 allotyping using neuraminidase treated plasma.[4] Two—homozygous deficiency at one C4 locus and two separate alleles present at the other; One—three separate alleles with one null allele deduced because of C4A/B densitometric ratios[4] of either 2 or ½; and zero—four separate alleles.

Recently we have examined C4 concentrations in 15 patients with insulin dependent diabetes mellitus selected according to whether they have zero, one, or two C4 null alleles. Four of five patients with two null alleles had C4 concentrations between 0·15 and 0·26 g/l, whereas all five patients without null alleles had concentrations between 0·41 and 0·67 g/l. The group with one null allele was intermediate.

There can be little doubt that C4 null alleles are at least partly responsible for the relatively low C4 concentrations found by Dr Vergani and others in insulin dependent diabetes mellitus. Other factors may also be implicated (for example, rate of consumption and synthesis), but we see no cause to postulate

additional genetic factors on the present evidence. If a search for such factors is undertaken we would urge that allowance be made for the contribution of the C4 loci within the major histocompatibility complex.

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Lymphomatoid granulomatosis

SIR,—Dr A D J Pearson and others make the bold statement that lymphomatoid granulomatosis has not been reported in Britain (23 April, p 1313). A more careful search of the dermatological published work would have shown that this comment is incorrect.[1 2] The occurrence of lymphomatoid granulomatosis in a 10 year old boy should not be entirely surprising as Liebow's original paper included a case in an eight year old girl.[3] Similarly, Liebow included descriptions of Bell's palsy and sialadenitis.[3]

Dr Pearson and others consider it unlikely that lymphomatoid granulomatosis has been mistaken for other forms of lung disease. We disagree with this statement as review of the published work shows the protean manifestations of lymphomatoid granulomatosis. Certainly, pulmonary features are the most common, and chest physicians should be fully conversant with the disease. We are aware of at least one local case where the diagnosis was initially thought to be carcinoma of the lung. In addition, the dermatological, neurological, and general medical features are so variable that the diagnosis can easily be missed in the absence of tissue biopsy. Indeed, one 34 year old man under our care, who presented with a deep ulcerated skin lesion, required several skin biopsies before the diagnosis of lymphomatoid granulomatosis was established. The characteristic angiodestructive nature of the atypical lymphohistiocytic infiltrate had produced large areas of ischaemic necrosis and consequently we had difficulty obtaining viable tissue.

It is important to look for skin lesions when the diagnosis of lymphomatoid granulomatosis is suspected as skin biopsy may obviate the need for percutaneous, transbronchial, or open lung biopsy. Cutaneous involvement is the commonest extrapulmonary manifestation of lymphomatoid granulomatosis. More than one third of patients have an erythematous rash or skin nodules, and the cutaneous signs may precede, appear simultaneously, or follow the development of pulmonary lesions.[4]

The cause of lymphomatoid granulomatosis remains obscure. Immunological investigations in the patient seen by us, however, have provided information on possible pathogenetic mechanisms. Immunoperoxidase studies on the tissue showed the presence of numerous histiocytes and T4 (helper) lymphocytes but few T8 (suppressor) cells; most plasma cells were polyclonal, but a focal aggregate containing a λ monoclone was also present. Examination of peripheral blood T lymphocytes showed a high T4:T8 ratio owing to low numbers of T8 (suppressor) cells. Although the serum IgG and IgA concentration was raised, no monoclone was identifiable in the blood or urine. B cell stimulation by T4 (helper) lymphocytes may explain such rises of serum immunoglobulins in patients with lymphomatoid granulomatosis.[5] Similarly, the development of immunoblastic lymphoma in lymphomatoid granulomatosis may be viewed as a natural consequence of continued B cell proliferation.[6] In contrast to these findings, however, hypogammaglobulinaemia and increased T8 (suppressor) activity[5 7] have been described in other patients with lymphomatoid granulomatosis. Thus, although lymphomatoid granulomatosis seems to represent a specific histological entity, different immunological abnormalities can occur. It is unfortunate that such investigations were not performed in the case reported by Dr Pearson and others.

Although we are not aware of a reported case, lymphomatoid granulomatosis seems a possible candidate to develop in the acquired immunodeficiency syndrome.

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Alpha blockers and converting enzyme inhibitors

SIR,—The incidence of sedation from indoramin in recent trials has not been as high as that reported by Dr P C Ruben and Professor J L Reid (9 April, p 1192). Their observations are based on earlier studies. In several of these a higher starting dose of indoramin was prescribed, and titration, to control blood pressure, was carried out rapidly. An interim analysis of data from 1113 patients with hypertension treated with indoramin in a multicentre trial has shown the incidence of sedation to be 18%.[1] Other studies, as yet unpublished, show a similar incidence of this side effect (8-18%). In most cases sedation is mild or moderate and transient.

Failure of ejaculation is a pharmacologically predictable side effect of treatment with alpha blockers. In studies using indoramin for treatment of hypertension the incidence of this side effect varies from 0 to 100% but in most it is low (0-7%).[2-9] In the multicentre trial the incidence was 2·5%.[1]

Based on our experience with this drug we recommend that in the treatment of hypertension the initial dose of indoramin should not exceed 25 mg twice daily and titration to control blood pressure should be carried out every two weeks. Such a regimen has resulted in a reduction of side effects without loss of efficacy.

There is also evidence of a negative inotropic effect during the clinical use of this drug in hypertension. Coltart has shown no evidence of myocardial depression in volunteers given 10 mg indoramin, intravenously.[9] Studies in progress will, we hope, establish the benefits of the vasodilatory action of this drug in heart failure. The recommendation in our data sheet to use indoramin with caution in heart failure is a regulatory requirement until we have evidence of a beneficial effect.

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New drugs in respiratory disorders

SIR,—I would like to take issue with Professor D C Flenley (19 March, p 955) when he states that red tinted urine indicates compliance with rifampicin treatment and hence implies adequate serum concentrations of the antibiotic.

A few years ago I treated a 43·5 kg 35 year old Asian with extensive sputum positive pulmonary tuberculosis. After three weeks' treatment with rifampicin, isoniazid, and ethambutol at conventional doses, fever and malaise persisted. Treatment was supervised by experienced nurses and the urine was of the expected colour. One hour after 150 mg rifampicin the serum concentration was less than 0·6 mg/l. After a single dose of 600 mg the concentration of rifampicin was 3·4, 7·6, and 6·3 mg/l at one and a half, two and a half, and four hours respectively. The dose of rifampicin was increased to 600 mg daily and doses of the other antituberculous drugs were increased proportionally. The red colour of the urine did not change appreciably. Within