seminar, though they have equal access to funds in the locally organised research scheme and presumably encounter similar problems to those of hospital doctors.

Understandably, the seminar was better at identifying problems than at suggesting solutions, but a few kites were flown. The attitudes of NHS managers and of health authority members may be difficult to change, but one plan that would enhance the status of NHS research would be the hypothecation of specified sums for research purposes only from the money being redistributed under the RAWP scheme and linked to a system of monitoring the quality of work done. Another, more forceful suggestion was that the present permissive powers of health authorities to provide background support for clinical research should become mandatory and might be linked to the designation of a certain number of NHS beds for research purposes. Yet perhaps the most important contribution of the seminar was simply the opening up of these issues for debate, and the Oxfordshire Research Committee is to be applauded for its initiative.

Antibiotic-associated colitis —the continuing saga

Clostridium difficile and its toxin were first found in patients with antibiotic-associated colitis in 1978.[1-3] Antimicrobial treatment, by suppressing normal gut flora, is now thought to make some patients susceptible to colitis caused by this toxin. The origin of the infection is still uncertain, since the organism is probably carried by only a few people: *C difficile* has been found in the stools of less than 2% of healthy adults,[4] though possibly very small numbers of the bacteria may be undetected even with selective media. Some clustering of cases[5-7] suggests that cross-infection may be important—a theory borne out by experimental studies in hamsters, which when given clindamycin develop fatal inflammatory lesions of the ileum and caecum (similar in many respects to human pseudomembranous colitis), though only if *C difficile* is acquired from their environment.[3]

The antibiotics incriminated most frequently are clindamycin and lincomycin, which accounted for 80% of reports submitted to the Committee on Safety of Medicines from 1964 to 1978.[8] Ampicillin, tetracycline, chloramphenicol, cephalosporins, penicillin, co-trimoxazole, and metronidazole have also been implicated, ampicillin more often than the others.[9] The predominance of clindamycin probably reflects its potent activity against faecal anaerobes, which are noticeably suppressed in patients with pseudomembranous colitis.[10] Antibiotics that deplete the gut flora in this way may promote the proliferation of *C difficile* and lead to production of its toxin, which induces necrotising lesions in colonic mucosa. Physiological disturbances caused by ischaemia, neoplasms, or inflammation may make patients particularly vulnerable and probably contribute to the greater frequency of severe antibiotic-associated colitis in the elderly.

Neither duration of chemotherapy nor dose appears to influence the likelihood of colitis—even short courses of surgical prophylaxis have been implicated. There may, however, be an interval as long as four weeks between stopping an antibiotic and the onset of symptoms. Toxigenic strains of *C difficile* are usually resistant to many antibiotics; 30-40% are resistant to clindamycin[3 11]—and isolates from patients with antibiotic-associated colitis induced by clindamycin are invariably resistant. Selection of clindamycin-resistant strains seems likely to be promoted by widespread use of clindamycin in a community, especially if the organism can be transmitted from patient to patient (perhaps by means of equipment such as bed pans or sigmoidoscopes).

What are the important aspects of management? Early recognition is vital, and though the clinical presentation is not particularly distinctive certain features may alert the physician. Typically, a patient recently treated with antibiotics develops watery diarrhoea, sometimes with severe abdominal pain, fever, and leucocytosis.[12] Sigmoidoscopy and biopsy may be helpful, though some patients with pseudomembranous lesions in the colon lack typical changes in the rectum.[13] The presence of a faecal toxin neutralised by *C sordelli* antitoxin is diagnostic, and toxic effects are detectable in tissue culture usually within 24 hours. A Birmingham team, reviewing 66 cases of antibiotic-associated colitis,[12] confirmed the diagnosis by sigmoidoscopy in 49% of cases, histologically in 68%, and by detection of toxin in 78%. *C difficile* was cultured from almost 90% of patients, though in the absence of toxin isolation of the organism is not considered diagnostic.

Treatment with oral vancomycin has usually proved safe and effective, producing rapid resolution of symptoms and elimination of both *C difficile* and its toxin.[14] Vancomycin is effective where clostridial toxin has been identified but not in patients with other varieties of postoperative diarrhoea.[15] The best dose and length of course have still not been established, but doses of 125 mg six-hourly produce faecal concentrations much greater than the minimum required for killing *C difficile*[15]; they are usually given for five days. Vancomycin should be started as soon as possible, since damage from the toxin may not be reversed by chemotherapy.[16] In most cases withdrawal of antibiotics is also rational (indeed, some patients respond readily to this measure alone), though in some the treatment of a primary life-threatening infection is essential. Such patients should probably be switched to another antibiotic, with a narrow-spectrum activity against a known or likely pathogen.

Relapses have been reported,[17 18] and a persistent carrier state has been discovered in some patients who have had clostridial antibiotic-associated colitis.[5] *C difficile* is a spore-bearing organism whose spores may survive an initial five-day treatment with vancomycin to germinate after the course has been completed. These organisms remain susceptible to vancomycin, and possibly a second course of vancomycin should be given to destroy any residual pathogens. Patients who have had antibiotic-associated colitis and require further courses of antibiotics may justifiably be covered by vancomycin prophylaxis.[19] One solution to this problem could be development of a toxoid vaccine conferring immunity to *C difficile*. Metronidazole has proved less popular than vancomycin since it is so efficiently absorbed from the gastrointestinal tract that very little drug remains in the gut lumen. It is, however, much cheaper than vancomycin, and has been used successfully.[20]

Patients with antibiotic-associated colitis should be nursed with the same precautions as others with enteric infections. In particular, sigmoidoscopes should be decontaminated by immersion for at least three hours in a sporicidal disinfectant such as glutaraldehyde.

C difficile and its toxin have also been implicated in exacerbations of chronic inflammatory bowel disease.[21-23] Disturbances in the gastrointestinal tract caused by inflammation could perhaps dispose to this infection. Nevertheless, sulphapyridine, a metabolite of sulphasalazine, cannot be entirely dismissed as a possible culprit (it may be particularly important in slow

acetylators); further assessment is needed of this possibility in patients with exacerbations of chronic inflammatory bowel disease unresponsive to standard medical treatment.

Lishman and his colleagues[24] recently examined the range of antibiotic-associated diarrhoea and found that some patients remained clinically well despite high concentrations of faecal toxin. Ten of 53 patients with antibiotic-associated diarrhoea were excreting toxin (though only one patient had histological evidence of membranous colitis). A control group of 53 patients who had been given antibiotics but who did not develop diarrhoea were also tested; of these, four had faecal toxin. Titres of toxin in both groups were within the same range, suggesting that factors other than concentration of the toxin influence the response. Elderly patients, who are at greatest risk of severe antibiotic-associated colitis, may have low resistance to effects of the toxin. The disease has a wide variety of clinical manifestations, ranging from an asymptomatic carrier state to fatal—but fortunately rare—pseudomembranous colitis. The pathogenesis of antibiotic-associated diarrhoea in most patients, in whom faecal toxin cannot be identified, remains unexplained.

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Regular Review

Management of asthma in the child aged under 6 years

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Asthma presents specific problems of management under the age of 6 years. These have proved difficult to overcome, but recent progress has been made with better definition of the parts played by allergy and viral infection. The development of methods of measuring pulmonary function at this age has increased the effectiveness of treatment. These advances have improved our understanding of what lies beneath that cloak for diagnostic ignorance, wheezy bronchitis, and thereby have produced a more rational approach to treatment.

Under about 18 months of age most children with wheezy bronchitis do not respond to bronchodilator agents.[1-3] After this age most do respond to such drugs and, indeed, their response to exercise and drugs shows that there is excessive bronchial lability, as in the older child with asthma.[4 5] In both age groups viral infections are the most frequent precipitants of attacks under 6 years.[6-9] Similar viruses have been recovered from children with wheezy bronchitis and from those with other respiratory tract infections, which suggests that the difference between children who wheeze and those who do not in response to an infection is not determined by the infecting agent.[10 11]

Among those children with wheezy bronchitis whose symptoms start in the first year of life there are some who are not going to be asthmatics and will cease to have these attacks perhaps in the second year. Others, however, will become asthmatics but the proportions have not been determined. Bronchodilator agents are not likely to be effective in these children, though they may be worth trying. The persistence of attacks beyond the second year points strongly to asthma, and these children will benefit from bronchodilator agents.