in our present armament is in treating infections caused by filamentous fungi, *Aspergillus* and the phycomycetes, and there is little evidence that the newer compounds are better than amphotericin or even as good.

Most effort has been given to the development of the imidazoles—clotrimazole, miconazole, econazole, and ketoconazole. Clotrimazole has good activity against filamentous fungi as well as yeasts when given by mouth but it has proved too toxic to be marketed for systemic use. It is possibly the best topical antifungal agent now available (though in the dermatophyte infections systemic griseofulvin still has a paramount part to play).[15] The other imidazoles, including miconazole, still require further systemic evaluation, as many of the contributors to the symposium emphasised. Miconazole is effective in coccidioidomycosis, a rare condition in Britain. When it is given by mouth blood concentrations of the drug are low and variable, and it is not active by this route in generalised candidiasis, though this is implied in one of the papers. In systemic infection miconazole has to be given parenterally, and no clear impression has yet emerged of its efficacy. In view of the evidence from laboratory studies of antagonism when combined with amphotericin[16] the two should not be used together. Ketoconazole when given by mouth seems to be absorbed more reliably but unfortunately its activity against *Aspergillus* species is variable and overall low.[17] Clearly much more work remains to be done on the imidazoles.

In the mean time, the best prospect for systemic mycoses remains the early use of amphotericin by all appropriate routes, and for this we urgently need better techniques for early diagnosis. Finally, some fungal infections will not respond to antibiotics alone: prosthetic endocarditis, for example, requires combined treatment with reoperation.[18]

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Investigating constipation

The Frenchman is obsessed by his liver, the Arab by gases in his stomach, the Englishman by his bowels. From infancy the British are brought up to regard a daily bowel action almost as a religious necessity and to believe in autointoxication from the cesspool of the unemptied colon; so it is little wonder that their doctors see vast numbers of patients obsessed with the frequency, consistency, diameter, and appearance of their stools. Unfortunately, hidden among these hordes, whose lack of bowel actions merely signifies the effects of their modern refined diet or disguises an underlying depression or anxiety state, are occasional exceptions with serious organic disease. How can they be identified?

As so often is the case, a careful history and examination will indicate the answer in most patients with constipation. The commoner organic causes are: obstruction of the lower bowel—for example, by a carcinoma of the colon or by diverticular diseases; painful anal conditions such as fissure in ano; or an adynamic bowel, as seen in Hirschsprung's disease or as the result of taking drugs that decrease the peristaltic activity of the bowel.

The possibility of a carcinomatous stricture of the colon should always be considered when a patient—particularly one over the age of 40—who has previously had a regular bowel habit develops constipation of increasing severity or, indeed, when a habitually constipated individual finds that his symptoms have become worse without obvious cause. The constipation may alternate with what the patient calls diarrhoea but which is usually the frequent desire to defecate or the passage of mucus in the stool. An obvious warning sign is the presence of fresh or altered blood in the faeces, and the patient may also have abdominal distension, colicky pain, and (usually as late manifestations) loss of appetite, loss of weight, and anaemia.

On abdominal examination a mass may be palpable due to the tumour itself or to faeces impacted above the growth. On rectal examination a tumour in the sigmoid colon may sometimes be felt through the wall of the rectum. An occult blood test on the faeces is often positive. In such cases sigmoidoscopy is mandatory, and indeed about a third of all growths in the large bowel can be seen with the instrument. Even if the tumour is not seen, suspicion may be aroused if blood or slime is seen in the lumen of the bowel, suggesting a more proximal lesion. The next step is a barium enema examination to clinch or refute the diagnosis. Colonoscopy is being used increasingly as another valuable means of making an exact diagnosis. Diverticular disease of the sigmoid colon can mimic carcinoma exactly in its clinical features. The barium enema examination will usually decide between the two but the radiologist may have difficulty in distinguishing the cause of a sigmoid stricture. Furthermore, these two common conditions may coexist. Less common causes of obstruction include Crohn's disease of the large bowel, a stricture complicating ulcerative colitis, and obstruction due to an extracolonic mass such as a pelvic tumour. Any painful anal condition (such as a fissure in ano or strangulated piles) may inhibit defecation and so precipitate constipation, but a careful local examination should soon establish the diagnosis.

In Hirschsprung's disease the history usually dates to the first month of life. The abdomen is greatly distended and the patient may have eversion of the umbilicus and widening of the subcostal angle. Nevertheless, the diagnosis is occasionally not recognised until adult life. The barium enema examination

shows gross dilatation of the colon leading down to a narrow funnel in the aganglionic rectum.

Constipation in the elderly may be due to diminished motor activity of the bowel, and this also may be prominent in patients with hypothyroidism. Other, rarer causes include organic nervous diseases affecting the sacral nerve roots or the cauda equina—including spinal tumour, transverse myelitis, and multiple sclerosis. Almost always, however, there will be urinary symptoms and obviously abnormal neurological signs on examination. Finally, the doctor should make a careful inquiry about the use of medicines and tablets since many drugs have a constipating effect: codeine, morphine, ganglion-blocking agents, and antacids such as aluminium hydroxide are common examples.

Having excluded all possibilities in this check list of organic or mechanical causes of constipation, the medical practitioner now has one of his most common yet most challenging and difficult problems. He has to re-educate his patient away from a lifetime of preconceived ideas of the physiology of his large intestine, wean him from his ritual purgatives (which often themselves are responsible for many of the patient's symptoms), and convert him to a regimen in which the bowel actions are controlled by a sensible bulk diet.

Drug lag bad: drug lack worse

The delay in introducing new drugs in the United States compared with similar countries has become known as the "drug lag." Despite official claims to the contrary,[1] valuable drugs have been partially or wholly denied to the American people for long periods.[2] Critics have argued that the United States Food and Drug Administration has been depriving rather than protecting the public or even cynically avoiding risk by waiting to see what happens elsewhere.

The countries against which America is compared have also experienced increasingly stringent and bureaucratic regulation of drugs, and in the past decade the climate in which pharmaceutical research is conducted has steadily deteriorated.[3] Britain is often used as the baseline for estimating the drug lag. Here people are particularly concerned over the difficulty and delay in starting early small-scale clinical trials[4]—contrary to scientific logic and despite their remarkable record of safety.[5]

America is of overriding importance to the pharmaceutical industry. It represents 18% of the world drug market and no international manufacturer can afford to ignore it. Yet the Centre for the Study of Drug Development has reported that between 1974 and 1976 the number of new chemical entities reaching clinical study in the United States fell by nearly half. The few that survive now take about nine more years to reach the market. The nominal life of a US patent is 17 years but the delays imposed by regulatory agencies made the average patent life 13·8 years in 1966 and only 8·9 years in 1977. By 1976 the average cost of marketing a new product had risen to over 50 million dollars.[6] Not only have research costs increased rapidly, but the proportion devoted to innovation has been reduced, as has the amount of support for basic research from both industrial and non-industrial sources. The implications for future therapeutic progress are plain to see.

Drug regulation is the most important determinant of the climate of research but other factors include economic, political, ethical, and legal restraints. The introduction of strict product liability could pose a huge additional burden and one that cannot yet be estimated. These restraints limit research options to such an extent that the problem has ceased to be simply a drug lag, which is relative: it has become an absolute lack of many types of new products.[7] For some years the development of drugs for rare diseases or for diseases that are common in poor countries has been economically profitless even when technically possible.[8] Manufacturers are driven to concentrate their efforts in progressively fewer and often the same areas, which are not always where the need is greatest. Some have already learned the hard way that it is unrewarding to develop the *n*th beta-blocker or non-steroidal anti-inflammatory agent.

If present trends continue the pharmaceutical industry, which depends heavily on research for its prosperity, seems certain to run down in the coming decade, with serious direct and indirect consequences. Increasing diversification by the big companies already shows their lack of confidence in the future. The trends will be difficult to counteract. Many of the contributory factors are themselves socially desirable, but a growing body of informed opinion holds that the pendulum has swung too far and that the problem must be tackled, whatever the difficulties.[9]

The Council for International Organisations of Medical Sciences (set up by WHO and UNESCO in 1949 as a federation of national and international biomedical organisations: address care of World Health Organisation, CH-1211 Geneva 27) recently adopted a special programme with the title "Drug Development and Use—Medical, Social, and Economic Implications." It has the support of WHO, of the International Union of Pharmacology, and of a broadly based international advisory board. The start of the new decade is a very suitable time for a reappraisal.

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