NORMAL FINDINGS

Management of patients in whom satisfactory and careful colonoscopy has failed to show a lesion remains a problem. It is usually possible to be fairly confident that an important lesion has not been missed on colonoscopy, but if the examination is less than satisfactory a repeat examination may be considered. We know of four patients in whom colonoscopy failed to show a colonic lesion responsible for the bleeding—one had a carcinoma of the appendix, one a carcinoma and one a villous adenoma (both of which were hidden in a caecal recess) and one an undetected polyp proximal to an acute splenic flexure. This is a further argument for preceding endoscopy with good radiology whenever possible, though only the last of the four lesions mentioned above was visible subsequently on repeat barium-enema examination.

Discussion

Although this series is reported from a specialised hospital and is therefore selected, the results are similar to those of others.⁷⁻¹⁶ All our patients underwent careful anorectal examinations to exclude local conditions and proctoscopy and sigmoidoscopy with rigid instruments, which are essential investigations before colonoscopy. A limited examination with an expensive fiberoptic sigmoidoscope and an examination with the longer colonoscope are both skilled procedures, and in this series 13 unsuspected neoplasms (20%) were proximal to the splenic flexure. In 133 of our patients (56%) colonoscopy showed that no abnormality was present, and this in itself has clinical value. We therefore believe that total colonoscopy is essential in high-risk patients such as ours.

Should colonoscopy replace barium-enema examination as the investigation of choice in such patients? We think not; double-contrast radiology remains a most valuable procedure.

It may show the cause for bleeding, it shows the overall configuration of the colon, which alerts the endoscopist to possible problem areas, and in some cases, in which colonoscopy is technically difficult, it allows the endoscopist to limit his examination. While colonoscopy should not be a substitute for inadequate radiological investigation, it seems more appropriate than repeating a barium-enema examination in patients with rectal bleeding; it should certainly replace diagnostic laparotomy, for it is safer, quicker, and more accurate.

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Epidemiology for the Uninitiated

Experimental studies

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Epidemiological studies of causation, such as we have outlined in preceding articles, rarely incriminate a factor to the extent that immediate action to remove or control it in the environment is justified. The evidence linking lung cancer and cigarette smoking is exceptional in this respect. Among additional kinds of evidence which may be brought to bear are the results of some form of experiment in which a group of people is removed from exposure to the factor and their subsequent disease experience compared with that among people in whom exposure

continues. Historically such experiments have provided compelling proof of causation, confirming, for example, the dietary origins of pellagra and the link between retrolental fibroplasia and oxygen treatment. Nevertheless, they are not necessarily appropriate models for studies which are required today. For the diseases of industrialisation, such as ischaemic heart disease, there is no evidence of a single major cause whose manipulation would drastically reduce incidence. Rather, there appears to be an array of interacting causes, and experimental verification of any one of them would mean studying thousands of people.

Experimental evidence of a kind may be obtained by critical assessment of unplanned experiments. The table shows the rise in ischaemic heart disease mortality after softening of the water supply to Scunthorpe. The change in mortality is compared to that in the neighbouring town of Grimsby, where the supply was unchanged and where mortality fell slightly. The limitation of this kind of evidence is that comparison with Grimsby may be biased by many influences that affect deaths from ischaemic heart disease in the two towns and for which adequate allowance cannot be made during analysis.

Hopes for preventing diseases of industrialisation rest more

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Mortality changes in Scunthorpe after introducing public-water softening in 1958, compared with those in the neighbouring town of Grimsby where water remained hard¹

	Scunthorpe		Grimsby	
	1950-3	1964-7	1950-3	1964-7
Water hardness (ppm)	488	100	250	250
Cardiovascular deaths per 100 000 per annum	568	704 (+ 24%)	634	549 (- 13%)

¹Robertson, J S, *Lancet*, 1968, 2, 348.

on modifying personal behaviour, in respect of such factors as diet, smoking, and exercise, than on large-scale changes in the environment—such as control of atmospheric pollution—which have been effective in the past. In the absence of results from planned experiments, the benefits of changed behaviour may be assessed by comparing the experiences of people who elect to change with those who do not. Unfortunately, this self-selection of the experimental group introduces biases which may nullify any results. To take an extreme example, certain groups of people who stopped smoking subsequently had a higher mortality from cardiorespiratory diseases than those who continued to smoke. Presumably this indicates that people may change their smoking habits because of incipient ill health, rather than that it is harmful to stop smoking.

Assessing preventive measures

Strong reasons exist why the assessment of possible preventive measures should not depend solely on unplanned and imperfectly controlled experiments. Whereas in the past the consequences of mistaken conclusions about the effectiveness of preventive measures might not have been serious, this may no longer be so. Hitherto, the available methods of prevention have generally been removal of some noxious influence such as water pollution. Today, prevention may require introducing substances—fluoride in the water supply, polyunsaturated fats in the diet, oral contraceptives—whose long-term hazards cannot be known with certainty. Where positive measures, such as whooping-cough vaccination, were introduced in the past they were to combat diseases that were widespread and lethal. When the incidence of disease is lower the hazards of a preventive measure give more concern, and current reassessment of the justification for mass whooping-cough vaccination reflects this. This reassessment is feasible only in relation to those complications of vaccination that are acute and generally obvious. Assessment of long-term complications is not at present possible, and evaluating newer preventive measures, such as large-scale treatment for mild hypertensives, will pose formidable problems, because complications resulting from them may be long delayed.

Despite the difficulties, large-scale preventive trials must be carried out before introducing costly and possibly hazardous preventive services. Multifactor trials, in which people's behaviour is simultaneously modified in several different ways, are an approach to the prohibitive costs of mounting large-scale trials of the contribution of any single factor to the aetiology of multifactorial diseases. In the UK Heart Disease Prevention Project, for example, the participants receive screening and health education for a range of coronary risk factors. This trial will not measure the extent to which individual factors contribute to the aetiology but will quantify the overall effect of the regimen and provide a pragmatic guide to further action.

Preventive trials

Preventive trials on populations are analogous to clinical trials on groups of patients, and the basic methods are therefore well known. Nevertheless, the practical problems differ. Selection of

an experimental population, to be randomised into intervention and control groups, must be made in such a way that it is reasonably representative of the reference population to which the measure, if successful, will be applied. Although feasibility will, in part, determine choice of the experimental population this cannot be the sole consideration. A doubt about the World Health Organisation trial on clofibrate arises because many of the subjects were blood donors, whose representativeness of the reference population is questionable.

Preventive trials of measures such as health education campaigns may require random allocation of communities rather than individuals to the intervention and control groups. Thus in the Heart Disease Prevention Project participating factories are allocated to one or other group, receiving either a programme of screening for coronary risk factors and health education, or being left alone. As in clinical trials, once the two groups have been assembled it is necessary to ensure that by chance there are not important differences between them that might affect the incidence of the disease being studied. Thereafter it is necessary to ensure that the management of the two groups remains the same in respect of everything except the experimental measure.

There are numerous possible sources of bias in assessing the outcome of a trial—for example, it has been found that default from preventive trials is more likely in those who have not complied with the advice or treatment given. High follow-up rates are one protection against bias, and achieving this for many participants (18 000 in the Heart Disease Prevention Project) is a formidable task.

A positive outcome of a trial, in terms of decreased mortality or morbidity in the experimental group, will require balancing of the magnitude of the decrease against the costs of mounting a definitive service for the reference population. The statistical significance of a difference between the experimental and control groups will depend not only on the magnitude of the difference but on the number of participants. In a large trial a statistically significant result may fall short of what is of practical importance. Conversely, and more frequently, a difference large enough to be of practical importance may fail to achieve statistical significance in a small trial. A trial may have a negative outcome either because the preventive measures are inherently ineffective or because compliance with them is poor. Either way, that particular preventive programme has failed—but it is important that there should be provision in the trial for measuring compliance so that potentially effective methods are not prematurely discarded.

Eventually this series will be collected into a book and hence no reprints will be available from the authors.

A patient had a small thrombosis in a branch of the left retinal vein, which appears to have completely cleared up. Her family has a history of cardiovascular accidents. She has been taking an antihypertensive (debrisoquine sulphate) and a coronary vasodilator Persantin (dipyridamole). For how long should such treatment be continued?

Retinal vein thrombosis is more common in hypertensives than normotensives, but I know of no study showing that treatment of the blood pressure prevents recurrence, although one might hope that it would. As this patient is hypertensive, however, hypotensive treatment should be continued indefinitely because there is evidence that control of hypertension does reduce the incidence of morbid vascular events: this might be all the more important in this patient, who has a bad family history of cardiovascular accidents. There is no definite evidence that one hypotensive regimen is superior to another in reducing the cardiovascular mortality rate: but if this patient also has angina, as is implied by her treatment with dipyridamole, then long-term treatment with a beta-blocker alone might be more appropriate than the debrisoquine and dipyridamole regimen. The beta-blocker might also provide a more even 24-hour blood pressure profile less prone to fluctuations in pressure. In any event good control of the blood pressure should be attained.