Byar and his colleagues[5] have discussed in general terms the relative merits of different ways of assessing different medical treatments, and they concluded that "randomised clinical trials remain the most valuable method of evaluating the efficacy of therapies." Ten British and American statisticians have recently reached similar conclusions.[6 7]

Once the advantages of testing a new treatment by an RCT have been accepted, the next most important step is to ensure that enough patients are entered into the trial for the results to be statistically significant. This will depend more on the number of deaths (or other events of interest such as relapse) that are expected to occur than on the total number of patients with the disease being studied. At least 20 deaths are likely to be needed in a trial of a new treatment that prevents two-thirds of deaths (an unusually effective treatment), but as many as 100 or more deaths are likely to be needed in a study in which one-third of deaths are prevented. In spite of this, many trials are launched which are too small to be effective. For example, the protocols of 13 current British clinical trials of systemic chemotherapy in early breast cancer were recently surveyed.[8] Few patients are likely to be entered into each trial, and differences in protocol will make it difficult to compare the results. The value of chemotherapy in breast cancer may remain unresolved for longer than if all the centres had collaborated in one or two large trials.

The design, conduct, and analysis of RCTs have been extensively developed. Peto and his colleagues[6 7] have described these developments in a way that is understandable to people without statistical expertise. They describe how RCTs can be flexible and, for example, can test one "treatment concept" against another rather than one rigid "drug regimen" against another. Formerly many trials recorded (and some still do) only the proportion of patients who, for example, survive for a fixed interval of time, such as five years from the start of a given treatment. This technique, although simple and useful, is inefficient, since it ignores the total length of time patients have survived—that is, it ignores information from patients studied for less than five years and the extra information provided by patients who survived for more than five years. Both defects are overcome by using actuarial survival curves.

Nowadays it is generally unnecessary to randomise patients within separate groups according to prognostic factors, since these are better allowed for retrospectively in the analysis. Treatment allocation need not be 1:1; if it is more convenient a greater or smaller proportion of patients may be allocated to the new treatment than to the old, although it is usually unwise to use ratios more extreme than 1:2 or 2:1. Not all patients who present with the disease that is being studied in a clinical trial need be entered into it. This fact is not often appreciated, and clinicians sometimes feel they are damaging a trial by selectively excluding patients from entry. Once entered, however, patients must be followed up, even those who do not actually receive the allocated treatment.

Statistics cannot completely answer the question when an RCT should be analysed or stopped. Usually it is best not to analyse the results until a few dozen deaths have occurred. Sequential trials formalise the process of ensuring that when one treatment is much worse than another the trial will automatically be stopped early, although if there is actually no difference between treatments (or only a slight difference) sequential trials may require more patients than non-sequential ones. Sequential trials should normally be designed and analysed only with close statistical supervision.

There is little to be lost from using RCTs to study new treatments, and much to be gained: "Let us remember the number of drugs that have been roman candles, making a bright and beautiful flash for a short time and then burning out."[9] And how many new drugs (such as lithium for the treatment of manic depression) which were useful have been discarded or ignored for many years because their flash was not bright enough?

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Pelvic sepsis after hysterectomy

Hysterectomy is sometimes associated with postoperative pelvic sepsis—occasionally severe enough to threaten life. Lesser degrees of infection are commonly reported in terms of "febrile morbidity," variously defined but usually taken as a temperature raised above 100°F (37·8°C) on two consecutive days (excluding the first postoperative 24 hours) or raised for over 24 hours.

In general, the reported incidence of febrile morbidity after vaginal hysterectomy has been higher (ranging[1 2] from 13% to 77%) than after abdominal hysterectomy (when morbidity has ranged[3 4] from 3% to 41% in the absence of antibiotics). The organisms responsible for postoperative sepsis come from the vagina, which carries a spectrum of potential pathogens similar to that recoverable from the unprepared colon. In British practice disinfection of the vagina is usually limited to antiseptic swabbing just before surgery, but positive cultures of potential pathogens have been obtained from the freshly cut vaginal edge in 65% of patients after such preparation, in a study in which 59% developed a postoperative fever.[5]

Douching the vagina with antiseptic for one or two days before operation has been tried in an attempt to reduce the bacterial population. Gynaflex[6] and chlorhexidine[7] proved ineffective, but use of povidone iodine was associated with a significant reduction in postoperative morbidity.[7] A mixture of two triphenylmethane dyes, brilliant green and crystal violet (Bonney's Blue), has remained a popular preparation, though little work has been done on their use in the last 20 years. These dyes are bacteriostatic, mainly effective against Gram-positive organisms, and their action is inhibited by serum and other body fluids.[8]

Though use of povidone iodine seems to be the most effective method of lowering the bacterial count, it does not sterilise the vagina. Hence hysterectomy, especially by the vaginal route, must be considered to be an operation in a contaminated field. The use of prophylactic antibiotics remains contentious, especially in general surgery, where several investigations have failed to show any benefits and some have reported an increase in postoperative infections, especially after gastrointestinal operations. Superinfection with resistant organisms has been suggested as the explanation of this counterproductive effect.

Interest in the use of prophylactic antibiotics for major gynaecological surgery has recently been reawakened, particularly in the USA. When used at vaginal hysterectomy

cephaloridine,[9] penicillin and streptomycin,[2] ampicillin,[10] or tetracycline[3] have each been associated with a definite reduction in total morbidity, in fever, and in the incidence of severe infections. Similar reductions in morbidity were obtained in elective abdominal hysterectomy using ampicillin or tetracycline[11] and cephalothin.[4]

Serious complications have rarely been described from the routine use of prophylactic antibiotics in major gynaecological surgery, but Ledger and Puttler[12] reported two deaths from pseudomembranous enterocolitis in healthy women, which they related to the use of antibiotics: one patient was given ampicillin and kanamycin and the other a cephalosporin. Glover and Van Nagell,[10] who used prophylactic ampicillin, reported two patients requiring readmission for pelvic infection due to ampicillin-resistant organisms.

Many postoperative gynaecological infections are caused by non-sporing anaerobic bacteria normally resident in the vagina, such as *Bacteroides*, which invade injured tissue. Metronidazole is highly effective against such organisms, but because it is inactive against aerobic and facultative bacteria it has no effect on normal populations of these organisms. The use of prophylactic metronidazole has been found to be highly effective in preventing postoperative pelvic sepsis. So far as is known this drug is nontoxic and free from side effects.[13]

Preoperative vaginal preparation and prophylactic antibiotics are no substitute for good surgical technique. Nevertheless, information from these controlled clinical trials indicates that these measures may well provide additional protection of the patient undergoing hysterectomy.

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Colonoscopy

The development of fibreoptic endoscopic instruments has opened up a whole new and exciting world of direct inspection of the tubes and cavities of the body. Based on the pioneer work of Professor Harold Hopkins of the Department of Physics in the University of Reading, the ingenuity of the instrument maker combined with the imagination of the endoscopist has enabled much of the alimentary canal and its associated adnexa, the bronchial tree, the pleural cavity, the pelvic organs (and even the contained fetus), the urinary passages, the orifices of the head, and the cranial cavity to be inspected, photographed, and subjected to biopsy. Adhesions and ducts can be divided, sphincters split, and foreign bodies and polyps removed, and many procedures that once required major open operation can now be performed with considerable safety.[1]

The modern fibreoptic colonoscope with its manoeuvrable fourway angulated tip, air, water, and suction controls and biopsy facilities became generally available about seven years ago. It is undoubtedly more difficult to use than the gastroscope, but its value, in both diagnosis and treatment, is now well established. Examination is usually performed under sedation and is aided by image intensification *x*-ray control to check the position of the instrument. An experienced colonoscopist can reach the caecum in 95% of examinations, although this may take 40 to 60 minutes to achieve.[2]

The general indications for colonoscopy are now becoming apparent, and we must emphasise that this examination nearly always follows a careful barium enema study. The colonoscopist may be asked to examine an abnormal or equivocal area of colon shown by a barium enema examination; he may help when a patient with colonic symptoms such as rectal bleeding, diarrhoea, etc, presents no abnormal findings either clinically or on barium enema examination or sigmoidoscopy; his help may be needed in assessing some cases of inflammatory bowel disease; he can keep a careful eye on a colonic anastomosis to pick up early evidence of local tumour recurrence; and, finally, he can remove polyps of any size from any site within the colon.

Loose and Williams[3] studied 99 patients with colonic bleeding at St Mark's Hospital; all had normal barium enema findings and no significant anorectal lesion. In 81 patients colonoscopy found no cause for the haemorrhage. A significant lesion was found in the 18 remaining patients: two carcinomas, 12 polyps, two angiomas, an amoeboma, and one example of eosinophilic colitis. Teague *et al*[4] report a 50% success rate in finding the probable or definitive source of bleeding in 75 undiagnosed cases. Carcinoma was found in 14 and polyps in another seven; this high detection rate might have been lower if double-contrast barium enemas had been performed routinely rather than conventional barium enema studies. These authors point out another advantage of colonoscopy: a radiological diagnosis was refuted in 11 further patients and an unnecessary laparotomy avoided in seven of these.

Perhaps the most important aspect of colonoscopy is that polyps can be removed with the diathermy snare without the patient's having to undergo open surgery, and large series have now been reported.[5,6] Polyps may cause frank or occult blood loss, may be malignant, and are certainly potentially malignant. Before the advent of endoscopic polypectomy, the accepted management of polyps out of the reach of the sigmoidoscope was to advise operative removal if the polyp was over 1 cm in diameter—when there is a higher risk of malignancy—or to review the smaller polyps by yearly barium enema examinations with the prospect of eventual surgery if the lesions increased in size.[7] Beahrs and Sanfelippo[8] reported that polyps under 0·5 cm in diameter were never shown to be malignant, that 1% of those measuring 1 cm in diameter had undergone malignant change, and that 7% of polyps that had reached 1·5 cm in size were malignant. The technique of colonoscopic polypectomy requires considerable skill and is time consuming, but Williams and his colleagues[5] from St Mark's Hospital reported the removal of 300 polyps of up to 4·5 cm in diameter from 169 patients with no serious complications. One patient sustained a "closed" perforation, which was managed conservatively, and two others suffered haemorrhage. Of the 250 polyps retrieved for histological examination nine were carcinomatous.

As with every new and exciting technique, it is always wise