



This Week in the Journal

January 31, 2002

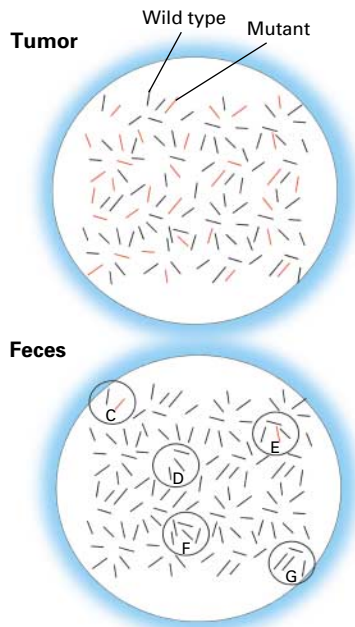
“Alternate-day hemodialysis should no longer be considered adequate for critically ill patients with acute renal failure.”

Daily Hemodialysis and Outcome of Acute Renal Failure

Morbidity and mortality among patients with acute renal failure are high, despite the use of renal-replacement therapies. This study investigated two regimens of intermittent hemodialysis — a daily regimen and an alternate-day (conventional) regimen — in 160 patients with acute renal failure. Survival two weeks after hemodialysis was the primary end point; the duration of acute renal failure and the rate of complications were secondary end points.

Daily hemodialysis was associated with better control of symptoms of uremia and longer survival than was conventional intermittent hemodialysis.

see page 305 (editorial, page 362)



Detection of APC Mutations in Fecal DNA

An early genetic change in the pathway to colorectal cancer is a mutation in the adenomatous polyposis coli (*APC*) gene. On the basis of the premise that cells with mutant *APC* genes are shed into the feces, these investigators devised a powerful molecular method to find such genes in feces from patients with colorectal cancer. Whereas feces from normal subjects had no detectable mutant *APC* genes, stools from over half the patients with colorectal cancer or colonic polyps contained such genes.

This study tested the feasibility of finding mutant APC genes in stools from patients with early colorectal cancer. The method developed for this purpose is a technical tour de force, akin to finding the proverbial needle in a haystack. Refinements of this method may lead to a specific and sensitive screening test for colorectal cancer.

see page 311 (Perspective, page 302)



Oral and Topical Corticosteroids for Bullous Pemphigoid

Bullous pemphigoid, the most common autoimmune blistering skin disease in elderly persons, is associated with substantial morbidity and mortality, in part owing to complications of systemic corticosteroid therapy. This randomized, multicenter trial compared treatment with oral prednisone and therapy with topical clobetasol propionate cream. The primary outcome was overall survival. Topical therapy significantly reduced mortality, the incidence of severe complications, and the length of hospital stays among patients with extensive disease.

Topical corticosteroids should be considered as standard treatment for patients with extensive bullous pemphigoid.

see page 321 (editorial, page 364)

PERSPECTIVE

A Needle in a Haystack of Genes

The holy grail of cancer screening is a sensitive, specific, and noninvasive test for the detection of malignant cells. Cytologic analysis of urine or sputum has not lived up to its early promise because it lacks sensitivity. Far more sensitive is the polymerase chain reaction (PCR), which replicates minuscule quantities of DNA to generate amounts that allow exact identification of tumor-specific mutations. Its success in detecting such mutations in exfoliated cells in the urine, sputum, pancreatic juice, and stools has been mixed, however, and the utility of the method in screening for cancer-specific mutations remains unproved.

Two genes, *K-ras* and *TP53*, which are commonly mutated in many types of cancer, illustrate the problem. *K-ras* participates in intracellular signaling; when mutated, it causes cells to behave as if they were under constant stimulation by a growth factor. Specific mutations of *K-ras* occur in colorectal cancer, but too inconsistently to serve as the basis of a screening test. *TP53* encodes p53, the guardian of the genome, and is the most frequently mutated gene in cancer. However, since almost 600 different mutations can occur in *TP53*, it has little value for screening.

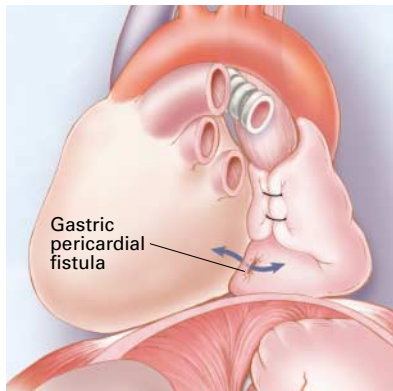
The APC Gene

The *APC* gene, by contrast, has considerable appeal for a screening test, because a mutation in *APC* is the earliest detectable molecular abnormality in both familial and sporadic colorectal cancer. The gene is large, and a variety of mutations can arise. However, about

83 percent of them cluster within a stretch of 1113 nucleotides, and almost all these mutations interrupt transcription of the gene. Hence, the mutant *APC* protein is abnormally short. The presence of a mutation can be inferred if a truncated *APC* protein is produced by an in vitro transcription-translation reaction. This protein-truncation test is a useful way of screening DNA extracted from lymphocytes for germ-line *APC* mutations in familial adenomatous polyposis.

The Protein-Truncation Test

Traverso et al. (see pages 311–320) used the principle of the protein-truncation test to develop a test for mutant *APC* genes within sloughed cells in stool (Fig. 1). Such a test might be used in noninvasive screening for colorectal cancer. This is easier said than done, however, because *APC* genes are rare in feces and mutant genes are even rarer — there is only about 1×10^{-13} mg of *APC*

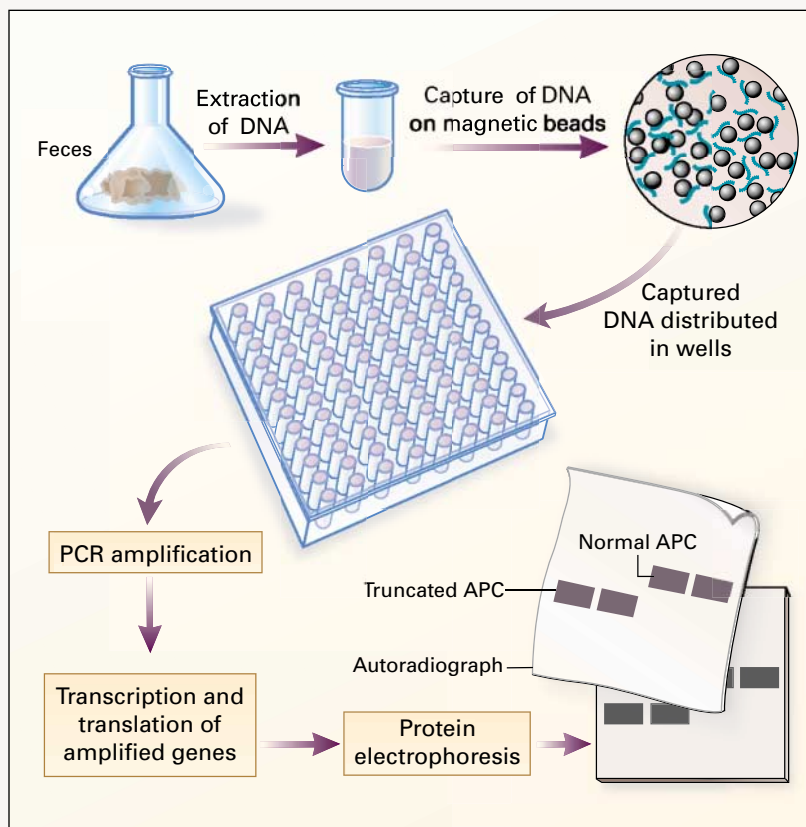


Gastropericardial Fistula after Laparoscopic Surgery for Reflux Disease

When patients with severe gastroesophageal reflux disease require surgery, the operation is frequently performed through a laparoscope. This case report describes a life-threatening gastropericardial fistula, which was a late complication of a laparoscopic Nissen fundoplication, as well as its repair.

Although gastropericardial fistula is rare, this report calls attention to the potential complications of laparoscopic antireflux surgery. Such complications might be minimized by improvements in surgical technique and additional training of surgeons who perform the procedure.

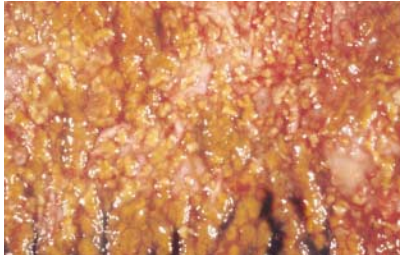
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DNA per milligram of stool. The challenges faced by Traverso et al. were the need to amplify this minute amount of genetic material despite the presence of inhibitors of the PCR in stool and the need to detect one truncated APC protein among the hundreds of normal APC proteins that would be produced during the protein-truncation assay.

Figure 1. Detection of Mutant APC Genes in Feces.

Oligonucleotide-coated beads capture APC genes and remove them from inhibitors of the PCR. After elution from the beads the APC DNA is distributed among the wells of a plastic plate in such a way that each well contains two to four APC genes. PCR is performed in each well, and the amplified genes are transcribed and translated in the presence of a radioactive amino acid. Electrophoresis and autoradiography reveal normal and truncated APC proteins.

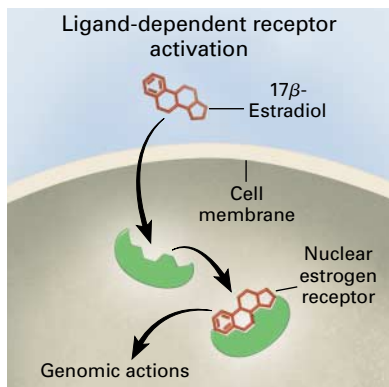


Clinical Practice: **Antibiotic-Associated Diarrhea**

A 53-year-old woman reports severe watery diarrhea with cramps. She is in her 7th day of a 10-day course of cefixime, prescribed for bronchitis. How should she be evaluated and treated?

This article reviews the evaluation and management of antibiotic-associated diarrhea, with particular attention to diarrhea associated with Clostridium difficile infection.

see page 334



Mechanisms of Disease: **Production and Actions of Estrogens**

Estrogens and estrogen-like substances are widely distributed in animals and plants, and it is now clear that estrogens have both nuclear and nonnuclear actions. This review article summarizes the production, metabolism, and actions of estrogens, with particular attention to the nuclear actions of estrogens and the mechanisms that underlie the different estrogen-agonist and estrogen-antagonist actions of selective estrogen-receptor-modulating drugs.

see page 340

That Traverso et al. found *APC* genes in all 74 stool samples they studied is a tour de force. However, mutant *APC* genes were detected in stool from only 17 of 28 patients with colorectal cancer and 9 of 18 patients with large colorectal adenomas. Moreover, of 12 cases of colorectal cancer in which the stool assay was negative, 6 involved tumors with truncating mutations. *APC* mutations were not detected in any control sample.

Although technically impressive, the method reported by Traverso et al. is clearly not ready for clinical application. We see it as a step in the arduous journey toward a reliable, noninvasive molecular screening test for colorec-

tal cancer. This journey merits encouragement because a convenient, specific, and sensitive noninvasive screening test for colorectal cancer should save more lives than current endoscopic methods. Traverso et al. have drawn back a curtain to reveal a tantalizing possibility, but there are other curtains and other possibilities. The basis of the next molecular screening test for colorectal cancer may not be a mutant gene but an abnormal protein that the new science of proteomics may find.

Medical papyri written by Egyptian doctors almost 4000 years ago advised physicians to “rise early . . . every day to see what has gone down from [the patient’s] anus. If it has gone

down like black lumps you shall say . . . his belly is in a bad state, blistered.” (*Ancient Egyptian Medicine*, British Museum Press, London, 1996). It will take time to determine whether molecular methods can improve on Theban medicine. Meanwhile, physicians are still looking at the stools of their patients, and they still worry when feces are black.

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