Drugs and sperm

A healthy man's sperm count may vary widely from month to month or even from week to week. The count is influenced by his health in the months preceding spermatogenesis and by events during the maturation of the spermatozoa. A low count may result from stress, disease, or drugs or may have no obvious cause.

Nevertheless, some effects of drugs are known. Hormones can influence the sperm count. Oestrogens, androgens, and some prostaglandins decrease spermatogenesis by lowering plasma gonadotrophin concentrations. The antioestrogens clomiphene and tamoxifen have been used to treat idiopathic oligospermia but with varying success. The antianidren-cyproterone acetate decreases the sperm count but seems unsuitable as a contraceptive for men because it affects potency and because the sperm count may increase again after prolonged treatment. Other problems with using steroid combinations as a “male pill” include their slow and inconsistent effects on the sperm count and their side effects.

Cytotoxic drugs cause oligospermia by directly affecting the germinal epithelium. Alkylating agents have a dose-related effect and may cause testicular atrophy, but function may regenerate many months after stopping treatment. Methotrexate given for psoriasis produces oligospermia, but plasma hormone concentrations remain normal: the oligospermia improves within a few months of stopping the drug. There are reports of azoospermia after administration of iodine-131 and during treatment with colchicine. Various toxic chemicals used in industry and agriculture have also come under suspicion, and the nematicide 1,2-dibromo-3-chloropropane has been identified (after 20 years of use) as a cause of oligospermia; this may be reversible if exposure is stopped in time. Excessive absorption of lead may affect the sperm count.

These effects are not unexpected, but more surprising is the influence of sulphasalazine. In the 1940s this drug was introduced for the treatment of ulcerative colitis, and in 1979 the first reports of oligospermia appeared (though it had already been suspected by some doctors). In these early reports six patients in America and four in England had oligospermia, which quickly improved when sulphasalazine was withdrawn—despite a worsening of bowel symptoms in some cases. Two more recent studies have added another 49 cases. In London 18 of the 28 patients had gross abnormalities of their semen but no endocrine abnormality: the semen improved two months after stopping sulphasalazine and 10 pregnancies occurred. In Glasgow 18 of the 21 patients had abnormal semen, and 15 had oligospermia. One patient discontinued treatment and had a normal semen analysis result two months later. The mechanism of the side effect is not clear, but it seems that either sulphasalazine or a metabolite is toxic to developing spermatozoa. This raises questions about those men who remain fertile while having treatment. In Glasgow five patients had become fathers while taking sulphasalazine; one baby was stillborn but the others were normal.

Reports on other drugs are few, and controlled trials are very few indeed. Psychotropic drugs, especially monoamine oxidase inhibitors, are thought to affect the sperm count adversely, but amitryptiline seems to improve oligospermia in some men: it is difficult to tell whether such effects are those of the drug or of the disease. There are unconfirmed reports of adverse effects from amoebicides, antimalarials, nitrofurantoin, reserpine, and co-trimoxazole. This last observation may be merely the effect of normal variation, and indeed co-trimoxazole is used to treat infertility related to chronic prostatitis. Cigarette smoking has been reported to increase the numbers of abnormal spermatozoa. The search continues for an agent which will lower the sperm count without other effects, and in the Far East hope is now centred on gossypol acetic acid, now being tested in China and India. Of more immediate concern, however, is the possibility—emphasised by the reports on sulphasalazine—that familiar drugs may have this side effect without it being recognised.
Duodenogastric reflux: is there any progress?

Human duodenogastric reflux has been recognised since 1833, when Beaumont1 noted regurgitation of bile into the stomach of his famous patient with a fistula (Alexis St Martin) when a thermometer was pushed against the gastric antrum or during "violent passion." Interest in the phenomenon has grown in the past 10-15 years, largely because of the possible association with gastric mucosal disease. The popular hypothesis2 is that the presence of duodenal contents in the stomach might damage the gastric mucosal barrier, which normally prevents back diffusion of hydrogen ion. This would produce mucosal damage, gastritis, and eventually gastric ulceration. Though attractive, this hypothesis remains unsupported by convincing experimental evidence. Many of the problems associated with the concept were discussed recently at the first international symposium on duodenogastric reflux.3

One of the interesting recent findings is that the retrograde passage of duodenal contents into the stomach is normal, both during fasting and after feeding. Evidence for this conclusion has come from direct sampling studies4 and from non-invasive techniques using a gamma camera to trace the passage of isotopes excreted in bile.5 In the fasted state most reflux occurs during the irregular contractile phase of gastroduodenal motility (phase 2).6 This refluxed bile, however, is rapidly cleared by the next phase of activity (phase 3), a period of regular, powerful propulsive contractions which empty the fasted stomach and sweep small-intestinal contents into the caecum. Reflux also occurs after feeding, but bile does not accumulate in the stomach because of continuing gastric emptying.

So, does the pylorus suggest that the contractions of the antrum and duodenum are not well co-ordinated?7 Duodenal reflux will occur, therefore, whenever duodenal contraction coincides with the pylorus being open, but because the retropropelled material is usually promptly returned to the duodenum bile does not accumulate in the stomach. If, then, the duodenal contents are to injure the gastric mucosa one or more of the following mechanisms must be postulated: greater than normal reflux, impaired gastric emptying, increased cytotoxicity of the refluxed material, or decreased gastric cytoprotection.

What evidence is there to incriminate any of the above factors in the pathogenesis of human gastric mucosal disease? Samples of gastric contents from patients with gastric ulcer contain more bile acid than those of normal controls even when the ulcer has healed,8 indicating greater reflux. Gastric emptying of a test meal in such patients, however, does not seem to be delayed,9 suggesting that the problem is not due to postprandial accumulation of bile. Their ability to clear bile refluxed in the fasted state, however, remains to be studied.

Studies on animals10 show that bile salts can break the gastric mucosal barrier and allow reverse diffusion of hydrogen ion, but long-term studies after cholecystogastric anastomosis show that the gastric mucosa adapts to the presence of bile salts so that neither histological gastritis nor gastric ulceration occurs.10 Duodenal juice probably contains injurious substances which have the potential to cause damage. Lysolecithin, for example, formed spontaneously from hydrolysis of biliary lecithin by pancreatic phospholipase,11 is highly cytotoxic, active at low pH, and may be recovered from the stomach after reflux. But there is no evidence that patients with gastric mucosal disease have either more aggressive duodenal juice or less robust cytoprotection than normal people.

The picture is different in patients who have had operations on the stomach. Intragastric bile is known to be injurious after partial gastrectomy and gastroenterostomy. In most such patients gastritis is found to be associated with the presence of intragastric bile, even in those without symptoms.12 This probably results from greater reflux after removal of the antrum and pylorus and from impaired emptying of regurgitated bile owing to the vagotomy. When patients who have had surgery complain of bilious vomiting and dyspepsia the solution is to perform an "anti-reflux" operation of the Roux-en-Y type. This undoubtedly improves the appearance of the gastric mucosa and usually also improves the symptoms.13

So, is there any practical significance to the finding of bile in the stomach? In the absence of any structural abnormality of the antropygic region the answer is probably no. Motor abnormality of the stomach or duodenum need not be suspected unless gastric emptying is obviously delayed, and, though coincident antral gastritis makes it tempting to relate the two findings causally, there is still insufficient evidence to do this with certainty. Such uncertainty also extends to treatment in non-operated patients, and more knowledge about the pathophysiology of reflux is required. Until then, patients with dyspeptic symptoms who happen to have bile in the stomach together with gastritis should continue to be treated in the conventional way, either with simple antacids (which also bind bile salts and lysolecithin) or with agents which improve gastric emptying, such as metoclopramide. Whether any improvement in these patients resulting from such treatment can be attributed to an effect on reflux, however, remains uncertain.

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