FIG 4—Total mortality and cardiovascular mortality in relation to cigarette smoking and other variables.

Discussion

Our data indicate that hypertriglyceridaemia definitely increases the probability of dying of cardiovascular causes in middle-aged men and that this effect is independent of serum cholesterol concentration, relative body weight, and smoking habits. This finding differs from the results of other prospective longitudinal studies that also used a multiple logistic risk analysis of data.^{3,4,7} These studies showed that serum triglyceride^{4,7} or $S_{120-400}$ (pre- β) lipoprotein³ concentration is related to coronary heart disease only through its association with serum cholesterol and has no predictive power over the latter variable. We cannot adequately explain this divergence of results. It should be noticed, however, that in the Framingham cohort a raised concentration of the triglyceride-rich $S_{120-400}$ lipoprotein was associated with a clearly increased risk of developing coronary heart disease³ in spite of the fact that this fraction accounts for only 10 to 20% of total serum cholesterol. The only prospective study that has so far shown an association between the serum triglyceride concentration and the incidence of ischaemic heart disease did not apply the multiple logistic model.⁶

Our results suggest that the relation between serum triglyceride concentration and CVM is not linear. Thus, the risk of CVM did not increase until values exceeded 1.7 mmol/l (150 mg/100 ml), a concentration often considered to be the upper limit of normal. In this respect triglyceride deviates from many other cardiovascular risk variables such as serum cholesterol, blood pressure, and cigarette consumption, which are

linearly correlated with disease events throughout the whole range without any critical level discriminating between safe and susceptible. Indeed, a pattern of association between triglyceride and ischaemic heart disease similar to that found here is evident also from the data of the Stockholm study,⁶ where a clearly increased risk was present only in the highest triglyceride quintile even though the authors suggested that there was a continuous linear regression. The basis for this difference in the risk profile of triglyceride and cholesterol is not known, but it might relate in some way to the differences in the metabolism of very-low-density and low-density lipoproteins.

The risk of CVM associated with raised serum triglyceride concentrations was considerably enhanced when some other abnormality was added. Highest incidence figures were found among the men who had a combination of hypertriglyceridaemia and obesity or smoking. In fact, obesity appeared to increase the risk of CVM sharply only in those men who had a simultaneous increase in concentrations of either of the serum lipids. This finding might account for the failure of many previous studies to show an association between obesity and cardiovascular disease.^{6,7}

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SIDE EFFECTS OF DRUGS

Anaphylaxis after dichloralphenazone treatment

There have been no reports of anaphylaxis after the ingestion of dichloralphenazone. A case is described of a patient who suffered this on two separate occasions.

Case report

A 66-year-old English pensioner, weighing 65 kg, was admitted for investigation of a minor haematemesis. His only history at that time was one of recurrent dysuria over the preceding 14 years, due to benign prostatic hyperplasia. He gave no personal or family history of allergy. On examination the only abnormality was a benign enlarged prostate.

On the night of admission he was given one dichloralphenazone (Well-dorm) tablet. This, together with 10 mg oral metoclopramide, which he had taken five hours earlier, was the only medication he received.

Adverse effect—Within 15 minutes of taking the tablet he complained of a generalised itch, and a diffuse erythematous rash with periorbital oedema was noted. He then complained of chest pain and collapsed unconscious with no measurable blood pressure. An electrocardiogram (ECG) showed atrial fibrillation. He was treated with intravenous hydrocortisone, intramuscular promethazine, and oxygen by facemask, and he regained consciousness within three hours. By the next morning he was well, and an ECG was normal.

On obtaining his past medical notes we discovered that an identical reaction had been described in 1963 again after the administration of dichloralphenazone, but in view of there being no reports of this reaction it was thought to be vasovagal syncope.

Comment

Dichloralphenazone is a loose complex that releases chloral hydrate in the gastric juice. Phenazone (antipyrine) is a pyrazolone derivative which has not been associated with the same severe reactions as the other pyrazolone derivatives, in particular amidopyrine, which in

one series was found to be an important cause of anaphylactic shock.¹ As anaphylaxis has not been reported with chloral hydrate the phenazone component was probably responsible for the reaction in our patient.

This case also illustrates the importance of reporting even the most unlikely drug reaction when no other satisfactory explanation can be found.

¹ Torok, H, *Dermatologia Internationalis*, 1969, 2, 57.

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Sulphasalazine-induced lupus syndrome in ulcerative colitis

We report here a patient who developed a lupus syndrome while receiving sulphasalazine. Although early reports recognised that sulphonamides could induce systemic lupus erythematosus (SLE),¹ later ones have implicated other drugs such as hydralazine and procainamide. Sulphasalazine, which is widely used in maintenance treatment of ulcerative colitis, is split by colonic bacteria into sulphapyridine and 5-aminosalicylic acid. The sulphonamide moiety is absorbed, and higher blood concentrations of sulphapyridine are attained in patients who are of "slow-acetylator" phenotype.²

Case report

In 1969 a 52-year-old woman developed increased frequency of bowel action, with associated loose stools containing mucus and blood. She had previously been well, apart from having undergone a thyroidectomy for thyrotoxicosis at the age of 21. One of her sons had had extensive ulcerative colitis since 1965 and had developed a hypersensitivity rash to sulphasalazine. She was also diagnosed as having ulcerative colitis and was treated with sulphasalazine until 1971 without apparent adverse effect. She was first seen by us in March 1972 when her symptoms had worsened. Sigmoidoscopy, rectal biopsy, and barium-enema examination confirmed active ulcerative colitis extending to the hepatic flexure, and treatment with sulphasalazine, 2 g/day, was started. Her symptoms remained troublesome, however, and prednisolone, 15 mg/day, was introduced in April 1972. The dose was gradually reduced, and the drug was discontinued in April 1974.

She remained in remission on sulphasalazine, 3 g/day, but began to complain of joint pains, and by October 1974 she had developed a non-deforming arthritis with active synovitis of shoulders, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and metatarsophalangeal joints. Bilateral knee effusions were also present. Treatment with ibuprofen, 1.2 g/day, was started, but the arthritis failed to improve. At this stage rheumatoid factor and antinuclear antibodies (ANA) were absent from the serum, but by January 1975 she had begun to develop Raynaud's phenomenon, and by June ANA were present in high titres with a homogeneous pattern. DNA antibody concentrations were raised (190 U/ml (normal: <25 U/ml)); differential agglutination titres, tests for LE cells (performed on four occasions), and anti-smooth-muscle and antimitochondrial antibodies gave negative results; C3, C4, and CH₅₀ values were normal; tissue-typing showed the presence of histocompatibility antigens HLA-A1, -A3, -B7, and -B8.

We thought that her illness might be a drug-induced lupus syndrome, so sulphasalazine was stopped in August 1975. The arthritis remained active, however, and in October 1975 she also had digital vasculitic lesions, although by January 1976 both of these conditions were resolving. During the acute illness her serum contained a mixed-component cryoglobulin, and ¹²⁵I-C1q binding activity³ was increased. This suggested the presence of circulating immune complexes, although renal and liver function test results, and muscle enzyme values were normal. Radiographs showed some small "hook" erosions in the metacarpophalangeal joints, similar to those seen in a Jaccoud arthropathy.⁴

Levels of DNA binding activity and ANA titres remained high for six months after sulphasalazine was stopped, but then fell to normal (fig 1). As the polyarthritis regressed the ulcerative colitis became more active, and maintenance treatment with prednisolone enemas 20 mg nightly proved ineffective. She refused to take systemic steroids, and in April 1976 azathioprine treatment was begun, but was discontinued after a month because of persistent nausea and vomiting. In May 1976 sulphasalazine, 3 g/day, was

FIG 1—Sequential study of clinical features (top), treatment (bottom), and changes in binding activity of double-stranded DNA (DS-DNA) and radioiodinated (¹²⁵I) complement (C1q).

reintroduced, with subsequent improvement of bowel symptoms. After two months, however, she again developed symptoms of active arthritis and synovitis, the DNA binding activity increased, and tests for ANA gave positive results. Sulphasalazine dosage was gradually reduced to 1 g/day, but joint symptoms persisted, and the drug was again withdrawn in January 1977.

Pharmacokinetics—Serum sulphapyridine concentration, measured when the patient was taking sulphasalazine, 2 g/day, was 213 μmol/l (53 μg/ml) (normal range: 80–201 μmol/l (20–50 μg/ml)). Her acetylator phenotype for sulphadimidine was determined⁵ a week after sulphasalazine had been withdrawn, and she was shown to be a slow acetylator.

Anti-DNA antibodies—Sera from 24 unselected patients with ulcerative colitis or Crohn's disease, who did not have joint symptoms, and who were on long-term treatment with sulphasalazine, 1–3 g/day, were tested for DNA binding activity. All had antibody concentrations within the normal range.

Comment

Although the patient did not fulfil the American Rheumatism Association's criteria⁶ for the diagnosis of SLE, she showed several features of a lupus syndrome while taking sulphasalazine—for example, polyarthrits, Raynaud's phenomenon, and vasculitis. High concentrations of ANA and abnormalities of DNA binding activity remitted when the drug was discontinued, but recurred when it was reintroduced—we therefore considered that the syndrome was drug-induced. The improvement after withdrawal of sulphasalazine in 1975 may have been due to the subsequent administration of prednisolone enemas, which are known to produce systemic effects.⁷ Nevertheless, the fall in DNA binding activity that occurred in 1976 was not associated with any change in treatment other than the reduction of the sulphasalazine dose.

Antibodies in patients with drug-induced SLE are usually directed against DNA nucleoprotein or single-stranded DNA⁸, and antibodies to DNA nucleoprotein are responsible for the finding of LE cells in such patients. Our patient is unusual in that antibodies against a well-characterised double-stranded DNA antigen⁹ were detected in high titres in the absence of LE cells. Our survey of other patients receiving sulphasalazine does not suggest that the presence of such antibodies is commonly associated with administration of this drug. Interestingly, changes in ¹²⁵I-C1q binding activity followed the same general pattern as changes in DNA antibody concentrations, suggesting that the DNA antibodies may have been partly responsible for the formation of circulating immune complexes. The absence of clinical evidence of renal disease in a patient with circulating DNA antibodies and immune complexes may seem surprising, but serum complement concentrations in our patient were consistently normal, and renal complications in SLE are more often seen in patients with hypocomplementaemia.¹⁰ Our patient's digital vasculitic lesions suggested that the circulating complexes had localised in medium-sized arteries, and this, in the absence of renal disease, suggested that the complexes were very large.¹¹

Alarcón-Segovia *et al*¹² reviewed possible associations between chronic ulcerative colitis, SLE, and the presence of LE cells. In several of their cases the now well-recognised association between ulcerative colitis and chronic active hepatitis in the presence of LE cells occurred. Four patients on sulphasalazine, however, developed arthropathy, polyserositis, and haematological abnormalities with positive test