References

- ¹ Slack J. Risks of ischaemic heart disease in familial hyperlipoproteinaemic states. *Lancet* 1969;ii:1380-2.
- ² Stone JJ, Levy RI, Fredrickson RI, Verter J. Coronary artery disease in 116 kindred with familial type II hyperlipoproteinaemia. *Circulation* 1974;49:476-88.
- ³ Mabuchi H, Ito S, Haba T, *et al.* Discrimination of familial hypercholesterolaemia and secondary hypercholesterolaemia by Achilles tendon thickness. *Atherosclerosis* 1977;28:61-8.
- ⁴ Bloch A, Dinsmore RE, Lees RS. Coronary arteriographic findings in type II and type IV hyperlipoproteinaemia. *Lancet* 1976;ii:928-30.
- ⁵ Huang TC, Chen CP, Wefler V, Raftery A. A stable reagent for the Liebermann-Burchard reaction. Application to rapid serum cholesterol determination. *Anal Chem* 1961;32:1405-7.
- ⁶ Anonymous. *Manual of laboratory operations, lipid research clinics program*. Vol 1. Lipids and lipoprotein analysis. DHEW Publications No (NIH) 75-628. Washington: DHEW, 1974.
- ⁷ Mjos OD, Thelle DS, Forde OH. Familial study of high density lipoprotein cholesterol and relation to age and sex. The Tromso heart study. *Acta Med Scand* 1977;201:323-9.
- ⁸ Jenkins MP. Selective coronary radiography. A percutaneous approach. *Radiology* 1967;89:815-24.
- ⁹ Beaumont JL, Carlson LA, Cooper GR, Feijar Z, Fredrickson DS, Strasser J. Classification of hyperlipidaemia and hyperlipoproteinaemia. *WHO Bull* 1970;43:891-908.
- ¹⁰ Falsetti HL, Schnatz JD, Green DG, Bunnell IL. Lipid and carbohydrate studies in coronary artery disease. *Circulation* 1968;37:184-91.
- ¹¹ Heinle RA, Levy RI, Fredrickson RS, Gorlin R. Lipid and carbohydrate abnormalities in patients with angiographically documented coronary artery disease. *Am J Cardiol* 1969;24:178-86.
- ¹² Barboriak JJ, Rimm A, Tristani FE, Walker JR, Lepley D. Risk factors in patients undergoing aorto-coronary bypass surgery. *J Thorac Cardiovasc Surg* 1972;64:92-7.
- ¹³ Barboriak JJ, Rimm AA, Anderson AJ, Tristani FE, Walker JR, Hemme RJ. Coronary artery occlusions and blood lipids. *Am Heart J* 1974;87:716-21.
- ¹⁴ Gotto A, Gorro GA, Thompson JR, *et al.* Relationship between plasma lipid concentrations and coronary artery disease in 496 patients. *Circulation* 1977;56:875-83.
- ¹⁵ Banks DC, Raftery EB, Oram S. Clinical significance of the coronary arteriogram. *Br Heart J* 1971;33:863-70.
- ¹⁶ Nitter-Hauge S, Enge I. Relationship between blood lipid levels and angiographically evaluated obstructions in coronary arteries. *Br Heart J* 1973;35:791-5.
- ¹⁷ Murray RG, Tweddell A, Third J, Hutton I. Relation between extent of coronary artery disease and severity of hyperlipoproteinaemia. *Br Heart J* 1975;37:1205-9.
- ¹⁸ Heiberger A. The risk of atherosclerotic vascular disease in subjects with xanthomatosis. *Acta Med Scand* 1975;198:249-61.
- ¹⁹ Beaumont V, Jacotot B, Beaumont JL. Ischaemic disease in men and women with familial hypercholesterolaemia and xanthomatosis. A comparative study of genetic and environmental factors in 274 heterozygous cases. *Atherosclerosis* 1976;24:441-50.
- ²⁰ Doyle JT, Dawber JT, Kannel WB, Haslin AS, Kahn HA. Cigarette smoking and coronary heart disease. *N Engl J Med* 1962;266:796-801.
- ²¹ Reid DD, Hamilton PJS, McCartney P, Rose G, Jarrett RJ, Keen H. Smoking and other risk factors for coronary heart disease in British civil servants. *Lancet* 1976;ii:979-84.
- ²² Gordon T, Kannel WB. Predisposition to atherosclerosis in the head, heart and legs. The Framingham study. *JAMA* 1972;222:661-6.
- ²³ Mustard JF, Murphy EA. Effect of smoking on blood coagulation and platelet survival in man. *Br Med J* 1963;ii:846-9.
- ²⁴ Hawkins RI. Smoking, platelets and thrombosis. *Nature* 1972;236:450-2.
- ²⁵ Meade TW, Chakrabarti R, Haines AP, North WRS, Stirling Y. Characteristics affecting fibrinolytic activity and plasma fibrinogen concentrations. *Br Med J* 1979;ii:153-6.
- ²⁶ Carvalho AC, Colman RW, Lees RS. Platelet function in hyperlipoproteinaemia. *N Engl J Med* 1974;290:434-48.
- ²⁷ Nordoy A, Rodset JM. Platelet function and platelet phospholipids in patients with hyperbetalipoproteinaemia: effect of nicotinic acid and clofibrate. *Acta Med Scand* 1971;189:385-9.
- ²⁸ Carvalho ACA, Lees RS. Platelets, intravascular coagulation and fibrinolysis in hyperlipidaemia: relationship to thromboembolic complications. *Acta Med Scand* 1979;suppl 642:101-2.
- ²⁹ Trayner IM, Mannarino E, Clyne CAC, Thompson GR. Serum lipids and high density lipoprotein cholesterol in peripheral vascular disease. *Br J Surg* 1980;67:497-9.
- ³⁰ Williams P, Robinson D, Bailey A. High density lipoprotein and coronary risk factors in normal men. *Lancet* 1979;ii:72-5.
- ³¹ Garrison RJ, Kannel WB, Feineil M, *et al.* Cigarette smoking and HDL cholesterol. The Framingham study. *Atherosclerosis* 1979;30:17-25.
- ³² Lim JS, Proudfit WL, Sones FM Jr. Left main coronary arterial obstruction: longterm follow-up of 141 non-surgical cases. *Am J Cardiol* 1975;36:131-5.
- ³³ Takaro T, Hultgren HN, Lipton MJ. The VA co-operative randomised study of surgery for coronary arterial occlusive disease. II. Subgroup with significant left main lesions. *Circulation* 1976;54:suppl III:107-17.
- ³⁴ Critten J, Waters DD, Theroux P, Mizgala HF. Left main coronary artery stenosis in young patients. *Chest* 1979;76:508-13.
- ³⁵ Allen JM, Thompson GR, Myant NB, Steiner R, Oakley CM. Cardiovascular complications of homozygous familial hypercholesterolaemia. *Br Heart J* 1980;44:361-8.
- ³⁶ Roberts WC. The status of coronary arteries in fatal ischaemic heart disease. *Cardiovasc Clin* 1975;7:1-24.
- ³⁷ Zahor Z, Czabanova V. Experimental atherosclerosis of the heart valve in rats following a long-term atherogenic regimen. *Atherosclerosis* 1977;27:49-57.
- ³⁸ Fry DL. Responses of the arterial wall to certain physical factors in atherogenesis: initiating factors. *Ciba Found Symp* 1973;No 12:93-125.

(Accepted 12 August 1981)

SHORT REPORTS

Treatment of erythema multiforme secondary to herpes simplex by prophylactic topical acyclovir

Erythema multiforme may occur repeatedly after recurrent herpes simplex lesions. There is considerable morbidity, and treatment is usually unsatisfactory. We report a case of intractable erythema multiforme after recurrent herpes labialis in which there was sustained benefit from prophylactic topical application of acyclovir.

Case report

A 51-year-old woman began developing erythema multiforme in 1976, coincident with her menopause. Each attack consisted of painful target lesions on the hands, feet, elbows, and knees, usually in association with oral, vaginal, and conjunctival ulceration, and sometimes with headache and general malaise. Attacks began 10 to 14 days after episodes of blistering and crusting around the mouth typical of herpes labialis. On several occasions herpes simplex virus was isolated from these lesions. Initially erythema multiforme occurred every few months, but the frequency and severity increased progressively so that by 1978 she was having erythema multiforme continuously.

Investigations for other possible causes of erythema multiforme were

negative. Clq-binding immune complexes were detected at the onset of erythema multiforme but total haemolytic complement, C3, and C4 concentrations were within normal limits. The herpes simplex complement-fixing antibody titre was 1/16 to 1/32. A succession of treatments had little or no effect. Idoxuridine 5% in dimethylsulphoxide reduced the severity of the herpes labialis but had no effect on the erythema multiforme; prednisolone 30 mg daily partially suppressed the erythema multiforme; and superficial radiotherapy (total dose 300 rads over four weeks) was followed by a remission lasting three months.

In February 1979, within two hours of the onset of herpes labialis, she was treated with intravenous acyclovir (Wellcome) 5 mg/kg eight-hourly for five days. One week later she suffered a further attack of erythema multiforme and a new outbreak of herpes labialis. In April she began applying 5% topical acyclovir around the mouth five times daily, but after four weeks this was reduced to twice daily. Subsequently she had only one attack of fully developed erythema multiforme, during a period of one month when she stopped using the cream. During the first 10 months of treatment there were several minor episodes of herpes simplex in the nostrils and occasional papular lesions of erythema multiforme on the fingers, but in the ensuing 10 months there were no further lesions.

Comment

A causal relation between erythema multiforme and herpes simplex infection has long been suspected clinically, though the pathogenesis is still not clear. Several studies have indicated that immune complexes

detectable in the serum are deposited in the skin transiently in the early stages of erythema multiforme, but the presence of herpes simplex antigen in such complexes remains in doubt.¹ Topical treatment of recurrent mucocutaneous herpes simplex lesions with antiviral drugs may reduce the severity of an individual lesion but has little effect on the associated erythema multiforme.

Acyclovir ointment is an effective treatment for ulcerative herpetic keratitis,² and intravenous acyclovir has proved beneficial as treatment^{3,4} and as prophylaxis⁵ for immune-compromised patients with herpes simplex lesions. In our patient early intravenous treatment was of no value but when prophylactic topical treatment was adopted the effect was dramatic. There had been no spontaneous remission in the previous three years and the longest period free of lesions was three months, after a course of radiotherapy. That erythema multiforme did not occur during either period when the patient was free of cold sores adds weight to the assumption that they are causally related.

The prophylactic effect of topical acyclovir in this patient was promising and there were no apparent side effects. A controlled trial is now in progress to evaluate the use of topical prophylaxis in patients with frequent mucocutaneous herpes simplex lesions accompanied by complications.

¹ Huff JC, Weston WL, Carn RI. Mixed cryoglobulinaemia, ¹²⁵I Clq binding and skin immunofluorescence in erythema multiforme. *J Invest Dermatol* 1980;74:375-8.

² Collum LM, Benedict-Smith A, Hillary IB. Randomised double-blind trial of acyclovir and idoxuridine in dendritic corneal ulceration. *Br J Ophthalmol* 1980;64:766-9.

³ Mitchell CD, Bean B, Gentry SR, Groth KE, Boen JR, Balfour HH. Acyclovir therapy for mucocutaneous herpes simplex infections in immunocompromised patients. *Lancet* 1981;ii:1389-92.

⁴ Chou S, Gallagher JG, Merigan TC. Controlled clinical trial of intravenous acyclovir in heart-transplant patients with mucocutaneous herpes simplex infections. *Lancet* 1981;ii:1392-4.

⁵ Saral R, Burns WH, Laskin OL, Santos GW, Lietman PS. Acyclovir prophylaxis of herpes-simplex-virus infections. *N Engl J Med* 1981;305:63-7.

(Accepted 18 August 1981)

St George's Hospital, London SW17 0QT

C T C KENNEDY, MA, MRCP, senior registrar (present appointment: consultant dermatologist, Bristol Royal Infirmary)

I M LEIGH, MB, MRCP, registrar (present appointment: senior registrar, St John's Hospital for Diseases of the Skin, London WC2H 7BJ)

H A RIDGWAY, MB, MRCP, registrar

M H WANSBROUGH-JONES, MSc, MRCP, consultant physician

Wellcome Research Laboratories, Beckenham, Kent BR3 3BS

D BRIGDEN, MB, MRCP, department of clinical immunology and chemotherapy

Chlorpropamide- and tolbutamide-alcohol flushing in non-insulin-dependent diabetes

Chlorpropamide through its effect in causing flushing after alcohol has been used to investigate the genetics of non-insulin-dependent diabetes.¹ Other sulphonylureas are also well known to cause alcohol flushing, though much less commonly. Only two out of 43 (4.7%) non-insulin-dependent diabetics treated with tolbutamide who attended our clinic during the past three months complained of a hot feeling in the face with visible flush after alcohol; other workers

have found a similar prevalence.² Since the relation between tolbutamide-alcohol flushing and chlorpropamide-alcohol flushing is not clear we challenged these two patients with alcohol after differing periods of treatment with tolbutamide, chlorpropamide, and placebo to see whether they produced flushing.

Case report

The two men, aged 55 and 58, had been diagnosed as having diabetes at the ages of 45 and 50 respectively. Neither had a family history of diabetes. One patient (case 1), who was 135% of ideal body weight, had been treated for a short while after diagnosis with a low-energy diet, but was later put on tolbutamide 250 mg three times daily, and good metabolic control resulted. The other patient (case 2), who was 95% of ideal body weight, had been treated with tolbutamide 500 mg twice daily as soon as diabetes was diagnosed and remained on this drug. Alcohol flushing tests were performed between 9 and 11 am after (a) two days of treatment and (b) long-term treatment with tolbutamide; after (c) two days, (d) seven days, and (e) 15 days of treatment with chlorpropamide 250 mg daily; and after (f) placebo. A four-day wash-out period preceded tests (b), (c), and (f).

For 30 minutes before and after ingestion of 40 ml sherry skin temperature was monitored (DOPT 100 digital thermometer, Milan) using a small temperature sensor probe fixed with adhesive tape to the left cheek. Room temperature was kept constant at between 20 and 22°C. Both patients' faces flushed, and they described a hot feeling in the face and showed a rise in skin temperature after both long- and short-term treatment with tolbutamide (table). Chlorpropamide-alcohol flushing occurred in only one patient, after 15 days' treatment. Neither facial flushing nor a significant (>1.2°C) temperature increase occurred after placebo.

Comment

The results suggest that, firstly, tolbutamide-alcohol flushing is not associated with a genetic type of diabetics and, secondly, chlorpropamide-alcohol flushing may occur in patients who show tolbutamide-alcohol flushing. Both sulphonylureas may interfere with alcohol metabolism, though this should not necessarily be regarded as a genetic marker for non-insulin-dependent diabetes. Thirdly, though flushing may not occur after challenge with one or two chlorpropamide tablets, it may appear after long-term treatment in diabetics without a family history of the disease. The differences found by several workers in the prevalence of chlorpropamide-alcohol flushing^{1,3} may thus be related to different durations of chlorpropamide treatment, suggesting that chlorpropamide-alcohol flushing depends partially on the body's metabolism of the drug.⁴ Chlorpropamide-alcohol flushing or tolbutamide-alcohol flushing may occur, independently of particular genetic predisposition, when a threshold circulating concentration of chlorpropamide or tolbutamide is reached. Thus longer treatment with chlorpropamide would probably mean that the patient who was still negative for chlorpropamide-alcohol flushing after 15 days of taking the drug would eventually become positive.

Flushing that is truly specific for genetic diabetes is likely to be due to some enzymatic inherited abnormality related to alcohol metabolism (alcohol dehydrogenase or acetaldehyde dehydrogenase) that is magnified particularly by chlorpropamide. An increase in acetaldehyde during the challenge test in patients positive for chlorpropamide-alcohol flushing⁵ could confirm this hypothesis and suggests that a quicker response (after a single tablet) should be present in strongly inherited diabetes whereas a delayed response could develop at any stage during long-term treatment. If this is not always true the reason is probably because these two different aspects—the body's metabolism of chlorpropamide and any enzymatic deficiency—are often variably combined.

¹ Leslie RDG, Pyke DA. Chlorpropamide-alcohol flushing: a dominantly inherited trait associated with diabetes. *Br Med J* 1978;ii:1519-21.

² O'Donovan CJ. Analysis of long-term experience with tolbutamide (orinase) in the management of diabetes. *Current Theories of Research* 1959;ii:69-87.

Facial skin temperature (°C) and the patient's subjective feeling of flushing after alcohol (40 ml) after treatment with tolbutamide, chlorpropamide, or placebo

	Tolbutamide				Chlorpropamide				Placebo			
	Long term		After two days		After two days		After seven days		After 15 days			
	Case 1	Case 2	Case 1	Case 2	Case 1	Case 2	Case 1	Case 2	Case 1	Case 2	Case 1	Case 2
Temperature (°C):												
Basal	33.5	31.8	33.2	31.5	33.5	32.1	33.2	32.3	33.7	32.1	33.4	32.0
Peak	36.0	33.7	35.8	33.9	34.5	32.5	34.0	32.8	35.9	32.9	34.3	32.6
Increase	2.5	1.9	2.6	2.4	1.0	0.4	0.8	0.5	2.2	0.8	0.9	0.6
Subjective feeling	+	+	+	+	±	—	—	—	+	—	—	—