preponderance of girls with defects of distant vision only. Another aspect of the difference between boys and girls was illustrated by the higher proportion of boys with unilateral defects of near and distant vision. Although we cannot explain this, amblyopia associated with squint may be a factor. The preponderance of adolescents from non-manual families with poor vision was due to the group with defective distant vision but normal near vision. The likely explanation is again the higher occurrence of myopia in non-manual families.[6 9]

Glasses had been prescribed for 18% of adolescents, 6% more than at 11 years, but a third of this group did not have their glasses available at the medical examination. Few adolescents seeing 6/9 or better with both eyes would welcome glasses or, arguably, would need them for medical reasons, yet 27% of adolescents prescribed glasses had normal distant visual acuity or only a minor defect and only a few of this group had defects of near vision alone. This group constituted 42% of those who failed to produce their glasses at the examination. Interestingly, fewer children with normal acuity were prescribed glasses in the northern region than elsewhere and significantly more girls than boys with normal vision possessed glasses. Distant visual acuity itself is clearly no guide to what is considered to be a need for glasses although it may indicate whether the glasses will be worn. It might be argued that these adolescents would see better with their glasses—that is, 6/5, which we did not record—but if this is so user rejection seems to indicate it is not desired by large numbers.

Further investigation is needed into the criteria on which glasses are prescribed and into the reasons for rejection by large numbers.

This study was jointly financed by the DES and the DHSS, whose support is gratefully acknowledged. We would also like to thank our colleagues at the National Children's Bureau for their helpful comments and Miss P Parekh for preparing the manuscript.

References

1 Davie, R, Butler, N R, and Goldstein, H, *From Birth to Seven*. London, Longman in association with National Children's Bureau, 1972.
2 Alberman, E D, Butler, N R, and Sheridan, M D, *Developmental Medicine and Child Neurology*, 1971, **13**, 9.
3 Peckham, C S, and Adams, B, *Child: Care, Health and Development*, 1975, **1**, 93.
4 Goldstein, H, in *Britain's Sixteen Year-Olds*, ed K Fogelman. London, National Children's Bureau, 1976.
5 General Register Office, *Classification of Occupations*. London, HMSO, 1966.
6 Douglas, J W B, Ross, J M, and Simpson, H R, *Journal of the Royal Statistical Society*, 1967, **130**, 479.
7 Tibbenham, A, Peckham, C S, and Gardiner, P A, *British Medical Journal*, 1978, **1**, 1312.
8 Goldshmidt, E, *Acta Ophthalmologica*, 1968, suppl No 98.
9 Peckham, C S, Gardiner, P A, and Goldstein, H, *British Medical Journal*, 1977, **1**, 542.

(*Accepted 2 March 1979*)

Controlled trial of plasma exchange in treatment of Raynaud's syndrome

M J G O'REILLY, G TALPOS, V C ROBERTS, J M WHITE, L T COTTON

British Medical Journal, 1979, **1**, 1113-1115

Summary and conclusions

Twenty-seven patients with Raynaud's syndrome had their digital vessel patency assessed by Doppler ultrasound after different thermal stresses. Digital vessel patency rates differed significantly after stresses at 15°C and 45°C. In a randomised controlled trial placebo and heparin had no effect either on patients' symptoms or on the patency of their digital vessels. Plasma exchange improved both symptoms and vessel patency rates at 15°C and 21°C. Improvement in seven out of eight of these patients has been maintained for six months.

Assessing digital vessel patency by Doppler techniques allows continuous, atraumatic, and safe evaluation of the effects of different methods of treatment on the patency of the digital vessels and has helped to indicate that plasma exchange is a useful adjunct in the management of patients with severe Raynaud's syndrome.

Departments of Biomedical Engineering and Haematology, King's College Hospital Medical School, London SE5
M J G O'REILLY, FRCS, honorary senior registrar
G TALPOS, MD, honorary registrar
V C ROBERTS, PHD, MIEE, senior lecturer in biomedical engineering
J M WHITE, MD, MRCPATH, professor of haematology
L T COTTON, MCH, FRCS, director of biomedical engineering

Introduction

Most studies have indicated that the symptoms and signs arising from Raynaud's syndrome are secondary to intermittent obstruction of the digital artery.[1 2] This obstruction leads to a decrease in local tissue perfusion, which can be assessed by digital plethysmography.[3] Plethysmography, however, is not entirely accurate[4] and is difficult to apply to assessing individual digital segments. Previously vessel patency has been identified only by arteriography,[5] often performed under general anaesthesia.[6] We have been able to assess patency in the digital arteries of each finger from the web to the terminal phalange with a conventional doppler velocimeter.[7] Since plasma exchange has been reported to be beneficial in managing patients with severe Raynaud's syndrome,[8] we performed a prospective trial to compare the effects of a placebo, intermittent systemic heparinisation, and plasma exchange on the patency of the digital vessels in 27 patients with Raynaud's syndrome. We also used the technique to observe the effects of thermal stresses on digital vessel patency.

Patients and methods

Twenty-seven patients with Raynaud's syndrome unrelated to any proximal vascular lesion or trauma to the digital vessels were entered consecutively into the trial and were randomly allocated to one of three treatments groups: (*a*) placebo (nine patients), two tablets twice a day for four weeks; (*b*) intermittent heparinisation (nine patients), 3000 IU intravenously each week for four weeks; (*c*) plasma exchange (nine patients), 2·0-2·5 l/week for four weeks, 70-75% of total plasma being exchanged on each occasion. Of the nine patients in the plasma

exchange group, one was later withdrawn after two plasma exchanges because no further plasma was available.

Vessel patency was assessed in a carefully controlled environmental temperature of 21°C before treatment, six weeks after treatment, and six months after treatment. A 10-MHz ultrasonic probe connected to a Parks 806A Doppler velocimeter insonated the digital arteries of each finger. Insonation proceeded from the proximal to the distal phalange. Each finger was divided into proximal, middle, and distal segments, each segment having a radial and ulnar digital artery. Thus each hand had 28 digital arteries available for insonation. Pulsatile arterial flow produced a doppler shift within the audio frequency range and readily detectable with this apparatus. Patency was defined in terms of the percentage of the 28 segmental vessels found to be patent on Doppler insonation.

Before treatment patency rates were also assessed after the hand had been immersed in water at 15°C and at 45°C for 60 seconds. At six weeks and six months after treatment patency was again assessed.

All patients underwent extensive haematological investigations to identify any connective tissue disorder presenting with Raynaud's syndrome.[9]

Results

Fig 1 compares the mean and standard deviation of the digital vessel patency rates before treatment at the three temperatures. These data were taken from all 27 patients. There was a significant difference between the patency at 21°C and the patency at each temperature stress (Student t test: $P < 0{\cdot}001$). Almost all our patients, irrespective of the underlying cause of their syndrome, showed that all their digital vessels could dilate in response to a warm stress. All patients showed a patency significantly lower than normal at the lower temperatures.

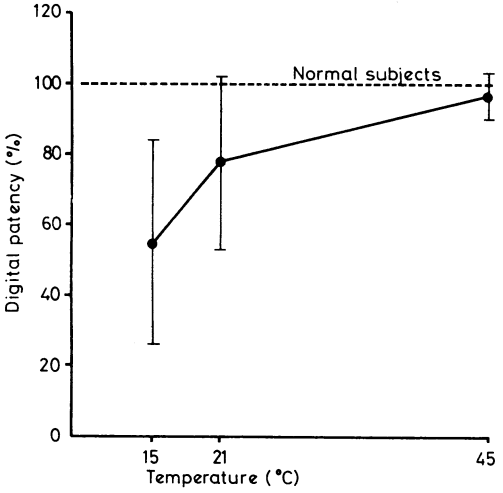

FIG 1—Digital patency as function of temperature in 27 patients with Raynaud's syndrome. Vertical bars indicate ±1 SD of mean.

None of the patients treated with placebo or heparin showed any symptomatic improvement or any increases in digital vessel patency rates after treatment. The changes in digital vessel patency rates in those treated with plasma exchange are shown in fig 2. There was a significant improvement at 21°C in percentage patency ($P < 0{\cdot}02$) at both six weeks and six months. At 15°C, percentage patency was also improved at both six weeks ($P < 0{\cdot}02$) and six months ($0{\cdot}02 < P < 0{\cdot}05$).

The table shows a summary of the findings in the patients treated with plasma exchange. Six months after the completion of treatment five of the eight patients treated with plasma exchange felt better, two felt the same, and one (case 8) felt worse. In seven cases vessel patency at 15°C was still better than before treatment: in the patient who felt worse the patency rate was unaltered. In three patients with chronic digital ulcers the ulcers healed and had remained healed six months after treatment. Two patients with connective tissue disorder improved symptomatically, one felt the same, and one felt worse.

Discussion

Our results show a Doppler ultrasound probe can provide an accurate estimation of the number of patent digital vessels in patients with Raynaud's syndrome, as the pulsatile arterial flow in the vessels is readily detected using the simplest of instruments. Ultrasound compares favourably with the more established and more complex techniques of plethysmography[10] or radioisotope clearance.[11] Our findings have also confirmed the original clinical work of Lewis,[1] who proposed that the symptoms and signs of Raynaud's syndrome arise in almost all cases from digital vessel occlusion and not from arteriolar occlusion. Furthermore, the additional insonation of the main limb vessels enables any concomitant occlusive lesions of these vessels to be quickly detected without resort to arteriography.[5]

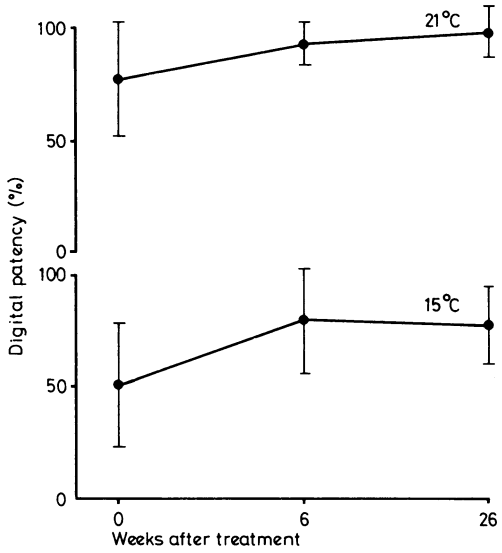

FIG 2—Digital patency at 21°C and after thermal stress at 15°C after plasma exchange in eight patients. Vertical bars indicate ±1 SD of mean.

Summary of findings in patients who underwent plasma exchange

Case No	Connective tissue disease	Ulcer	Cold patency (%) at 15°C at: 0	6 weekly	6 monthly	Symptoms
1			82	80	93	Improved
2			57	82	70	No change
3		+	37	100	91	Improved
4			20	86	86	Improved
5	+		66	80	79	No change
6	+		77	98	80	Improved
7	+	+	57	100	95	Improved
8	+	+	39	98	39	Deteriorated

Opinions vary about the correct temperature stresses that should be applied to these patients' digits so that the most accurate estimate of their digital vessel patency may be obtained.[12,13] We were surprised to find that after immersion of the hand in water at 45°C practically all the patients' digital vessels were shown to be patent. 15°C was chosen as the appropriate cold thermal stress as a result of the work of Shepherd[13] and Lottenbach,[14] who showed almost complete and persistent reduction in digital flow in patients with Raynaud's phenomenon when their hands were subjected to a stress between 10°C and 15°C. This temperature range was also confirmed by Sumner and Strandness.[4] Our findings of a very significant difference

in digital vessel patency rates between 15°C and 21°C justify using this thermal stress.

In our patients plasma exchange significantly improved digital vessel patency rates at both 15°C and 21°C. Plasma exchange is known to be a potent method of defibrination.[15] Furthermore, plasma fibrinogen is a major determinant of whole blood viscosity at low shear rates. Thus the concept that narrowed digital vessels, initially impassable to viscous blood, are able to transmit blood rendered less viscous by plasma exchange appears attractive. Nevertheless, like Browse[16] we cannot explain why short-term reduction in plasma fibrinogen concentrations results in a long-term symptomatic improvement, and, in our patients, also quantitative evidence of improvement. This long-term improvement may be explained partly by changes which have been observed in the deformability of the red blood cells,[17] but the possible role of circulating immune complexes[8] still needs clarification and is the subject of continuing investigation.

We thank the Medical Research Council, Mecca Ltd, and ICI Ltd for their generosity in supporting this investigation, and the many members of the department without whose help and encouragement this work would not have been possible.

References

1 Lewis, T, *Heart*, 1930, **15**, 177.
2 Porter, J M, *et al*, *Surgery*, 1975, **77**, 11.
3 Zweifler, A J, *et al*, *Angiology*, 1967, **18**, 591.
4 Strandness, D E, and Sumner, D S, *Haemodynamics for Surgeons*, p 550. New York, Grune and Stratton, 1975.
5 Yao, S T, *et al*, *Surgery, Gynecology and Obstetrics*, 1972, **135**, 373.
6 Kent, S J S, Thomas, M L, and Browse, N L, *Journal of Cardiovascular Surgery*, 1976, **17**, 72.
7 O'Reilly, M J G, *et al*, *American Journal of Physiology*. In press.
8 Talpos, G, *et al*, *Lancet*, 1978, **2**, 416.
9 Richards, R L, *British Journal of Hospital Medicine*, 1978, **19**, 513.
10 Lassen, N A, Krahenbuhl, B, and Hirai, M, *American Journal of Physiology*, 1977, **232**, 338.
11 Coffman, J D, and Cohen, A S, *New England Journal of Medicine*, 1971, **285**, 259.
12 Jamieson, G B, Lindbrook, J, and Wilson, A, *Circulation*, 1971, **44**, 254.
13 Shepherd, J T, in *Physiology of the Circulation in Human Limbs in Health and Disease*, p 279. Philadelphia, Saunders, 1963.
14 Lottenback, K, *Angiology*, 1971, **22**, 4.
15 Pinching, A J, *British Journal of Hospital Medicine*, 1978, **10**, 658.
16 Jarret, R E M, Morland, M, and Browse, N L, *British Medical Journal*, 1978, **3**, 523.
17 Dodds, A J, *et al*. Submitted for publication, 1979.

(*Accepted 7 March 1979*)

Indomethacin increases plasma lithium

J C FRÖLICH, R LEFTWICH, M RAGHEB, J A OATES, I REIMANN, D BUCHANAN

British Medical Journal, 1979, **1**, 1115-1116

Summary and conclusions

The effects of indomethacin on plasma lithium concentrations and renal lithium clearance were investigated in three psychiatric patients and four normal volunteers. After steady-state plasma lithium concentrations had been reached, the subjects received indomethacin placebo for three to seven days, indomethacin (50 mg thrice daily) for seven days, and placebo again for three to seven days. Indomethacin increased plasma lithium concentrations by 59% in the psychiatric patients and 30% in the volunteers. Renal lithium clearance was reduced by indomethacin by 31% in the group as a whole, and prostaglandin synthesis, determined by measuring the major metabolite of PGE_2 with mass spectrometry, was reduced by 55%.

These results show that indomethacin reduces renal lithium clearance to an extent which may be clinically important. They also suggest that the renal clearance may be affected by a prostaglandin-dependent mechanism, possibly located in the distal tubule.

Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany
J C FRÖLICH, MD, physician
I REIMANN, MD, PHD, physician

Departments of Medicine and Pharmacology, Vanderbilt University, Nashville, Tennessee, USA
R LEFTWICH, MD, physician
J A OATES, MD, physician
D BUCHANAN, PHD

Middle Tennessee Mental Health Institute, Nashville, Tennessee, USA
M RAGHEB, MD, physician

Introduction

Lithium is being given to increasing numbers of patients for the treatment of manic depressive and other psychiatric illnesses.[1] This treatment is not without hazards, and fatal lithium intoxication has been reported.[1] We describe here a drug interaction between lithium and indomethacin which could make the simultaneous administration of these drugs hazardous. We also provide evidence for a novel prostaglandin-mediated excretory mechanism of lithium.

Patients and methods

The study was carried out in three psychiatric patients in the manic phase of their disease and in four normal volunteers. The study was started when steady-state lithium concentrations had been reached, which usually required over three weeks of constant lithium intake in the patients and 10 to 14 days in the normal volunteers. Steady state was defined as plasma lithium concentrations on three consecutive days within 0·1 mmol(mEq)/l of each other. The patients and volunteers were kept on free diet throughout the study and received no other drugs.

The study consisted of three periods in which lithium intake was constant. In the first period an indomethacin placebo was given for three to seven days, in the second indomethacin was given in a dose of 50 mg three times a day for seven days, and in the third placebo was given for three to seven days. Throughout the study we determined plasma lithium concentrations daily 12 hours after the last dose and lithium and creatinine in daily 24-hour urine samples. On the last day of each period 7α-hydroxy-5, 11-diketotetranorprosta-1, 16 dioic acid (PGE-M) was determined by gas chromatography-mass spectrometry[2] to assess the rate of prostaglandin synthesis, and each patient underwent psychiatric evaluation on the brief psychiatric rating scale, sad-glad scale, and Minnesota personality inventory.