arterial pressure, causing natriuresis, which leads to depletion of sodium and further raises the angiotensin II concentration.⁵ Given that the blood pressure of patients with the hyponatraemic hypertensive syndrome is renin dependent, our patients' pronounced hypotensive response to atenolol is not surprising.

The correct management of patients with this syndrome is unclear. It is not known whether blood pressure falls precipitously in all patients who take β blockers or how far the risk of hypotension extends to those who take other classes of drugs. Bethanidine and captopril have been reported as causing serious hypotension,^{1,5} and we recommend that they be avoided as initial treatment.

We conclude that patients with malignant hypertension and hypokalaemia or hyponatraemia should be

treated with low doses of β blockers that can be raised according to the response of the blood pressure. Any precipitous fall in blood pressure can be reversed by a prompt infusion of saline, although temporary inotropic support may also be required.

- 1 Graham DI. Ischaemic brain damage of cerebral perfusion type after treatment of severe hypertension. *Br Med J* 1979;iv:739.
- 2 Ledingham JGG. Management of hypertensive crises. *Hypertension* 1983;5 (suppl III):114-9.
- 3 Isles CG, Johnson AOC, Milne FJ. Slow response nifedipine and atenolol as initial treatment in blacks with malignant hypertension. *Br J Clin Pharmacol* 1986;21:377-83.
- 4 Brown JJ, Davies DL, Lever AF, Robertson JIS. Plasma renin concentration in human hypertension. I. Relation between renin, sodium and potassium. *Br Med J* 1965;iii:144-8.
- 5 Atkinson AB, Brown JJ, Davies DL, et al. Hyponatraemic hypertensive syndrome with renal artery occlusion corrected by captopril. *Lancet* 1979;ii:606-9.

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Immune response of infants and preschool children to typhoid vaccine given intradermally or subcutaneously

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In developing countries typhoid fever is common not only in adults and children of school age but also in infants and preschool children, in whom the rate of complications and the case fatality rate may be as high as in older children.¹ Children should therefore be immunised against typhoid fever as early as possible. The immunogenic and protective efficacies of the currently available heat inactivated typhoid vaccine have been investigated only in schoolchildren and adults.²⁻⁴ We therefore measured its immunogenicity in infants and preschool children.

Subjects, methods, and results

From August 1985 to August 1986 infants (aged 6-11 months) and preschool children (aged 12-59 months) who had not been immunised against typhoid fever were recruited after parental consent had been obtained. The vaccine (King Institute, Madras) contained 500×10^6 heat killed *Salmonella typhi*, 250×10^6 heat killed *S paratyphi A*, and 0.5% phenol in 0.5 ml. Subjects recruited in alternate weeks were vaccinated subcutaneously, and the others were

vaccinated intradermally. Subcutaneous vaccination (0.5 ml) was given in the thigh, and intradermal vaccination (0.1 ml) was given in the volar surface of the forearm. The second dose was given four weeks later by the same route. Blood was collected before the first vaccination and four weeks after the second. The serum was separated, diluted 1/5 in isotonic saline, and stored at -20°C until tested.

Serum samples were tested in dilutions of 1/20 to 1/1280 for the presence and titre of antibodies to *S typhi* O and H antigens by tube agglutination with commercial antigens (Span Diagnostics, Bombay) and appropriate controls.⁵ Subjects whose samples at a 1/20 dilution did not contain antibody were considered to be negative for the antibody. If samples obtained from these children after vaccination contained antibody then seroconversion was considered to have occurred. The χ^2 test was used to compare rates of seroconversion and the two tailed Student's *t* test to compare the geometric mean titres of antibody.

Among the 363 subjects recruited into the study 289 returned for the second dose and 206 to give a blood sample after immunisation at the stipulated intervals; these 206 comprised 123 infants and 83 preschool children. The table shows the results. Of subjects who were initially negative for the antibody 60 of the 75 vaccinated subcutaneously and 70 of the 100 vaccinated intradermally developed antibodies to O antigen. This difference was not significant ($\chi^2=1.75$, $p=0.18$). The proportions of subjects who became positive for antibody to H antigen were also not significantly different between the two groups ($\chi^2=0.12$, $p=0.72$). In both vaccination groups, however, the proportion who became positive for antibody to H antigen was significantly higher than the proportion who became positive for O antigen ($\chi^2>15$, $p<0.001$). The proportion who became positive for antibody to O or H antigen among infants, 1 year olds, and 2-4 year olds by each route was not significantly different ($p>0.05$).

The geometric mean titres of antibodies to H antigen after intradermal or subcutaneous vaccination were significantly higher than those of antibodies to O antigen ($p<0.001$). There was no difference between the titres of antibodies to O or H antigen in those vaccinated subcutaneously and intradermally ($p>0.05$) or in the titres among infants, 1 year olds, and 2-4 year olds ($p>0.05$).

Comment

Overall the immune response of infants and preschool children to the heat inactivated typhoid vaccine given subcutaneously or intradermally

Rates of seroconversion and geometric mean titres of antibody to *S typhi* O and H in infants and preschool children after typhoid vaccination

Age (months)	No of children	Antibody to <i>S typhi</i> O		Antibody to <i>S typhi</i> H	
		No who developed antibody/No initially negative (%)	Geometric mean titre	No who developed antibody/No initially negative (%)	Geometric mean titre
<i>Subcutaneous route</i>					
6-12-24-59	52 23 20	40/51 (78) 13/14 (93) 7/10 (70)	80.0 84.4 65.6	52/52 (100) 22/23 (96) 19/19 (100)	265.5 411.7 222.0
Total	95	60/75 (80)	79.1	93/94 (99)	284.0
<i>Intradermal route</i>					
6-12-24-59	71 20 20	47/68 (69) 13/20 (65) 10/12 (83)	57.8 84.3 85.7	69/71 (97) 19/19 (100) 18/19 (95)	251.2 257.0 201.6
Total	111	70/100 (70)	65.6	106/109 (97)	244.7

was excellent. Infants do not respond well to purified polysaccharide antigens of pneumococci, meningococci, or *Haemophilus influenzae*. Although *S typhi* O is a polysaccharide, infants responded to it as well as older children, probably because it was presented as a whole cell antigen. *S typhi* H is protein, and the immune response was better.

New vaccines against typhoid fever are at various stages of development and evaluation. Until better vaccines are available the heat killed *S typhi* vaccine may be given, either subcutaneously or intradermally, starting at 6 months of age.

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- Christie AB. *Infectious diseases: epidemiology and clinical practice*. Vol 1. 4th ed. Edinburgh: Churchill Livingstone, 1987:100-64.
- Cvijetanic B, Uemura K. The present status of field and laboratory studies of typhoid and paratyphoid vaccines with special reference to studies sponsored by WHO. *Bull WHO* 1965;32:29-36.
- Rao MN, Sundari B, Shyamalamba CH, Rao PG. A study of antibody response to TAB vaccine in school children and its relationship to nutritional status. *Indian Pediatr* 1977;14:271-4.
- Ramakrishnan PS, Norman EJ, Krishnamurthy KA. A study of antibody response to TAB vaccination by subcutaneous and intradermal routes in urban school children. *Indian Pediatr* 1978;15:641-3.
- Cruickshank R, Duguid JP, Marmion BP, Swain RHA. *Medical microbiology*. Vol 3. 12th ed. Edinburgh: Churchill Livingstone, 1975:403-19.

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Serum gonadotrophin concentrations in men with peripheral vascular disease and impotence

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Impotence is a common problem in men with peripheral vascular disease. It is usually attributed to impaired blood supply to the penis due to arterial atherosclerosis^{1,2} and is associated with hypercholesterolaemia, smoking, and diabetes.³ We measured testicular function to test whether such patients may also have testicular ischaemia and hypogonadism.

Patients, methods, and results

Thirty two patients with peripheral vascular disease (age range 39-79) who had stable marital relationships and were not taking drugs which induce impotence were divided into two groups: those who complained of impotence (group 1; n=20) and those who claimed to have normal sexual activity (group 2; n=12). We also studied a control group of 20 men with minor illnesses attending a day centre or hospital outpatient department (age range 39-79).

Serum testosterone,⁴ luteinising hormone, and follicle stimulating hormone concentrations were measured by radioimmunoassay and sex hormone binding globulin concentration was measured by

immunoradiometric assay.⁵ Serum testosterone concentration was corrected to a sex hormone binding globulin concentration of 30 nmol/l (midpoint of the reference range for men).

Arteriography was performed in 17 of the impotent patients, and atheromatous disease was classified as aortoiliac in two, femoral in seven, distal in one, and diffuse in seven. Statistical analysis was carried out with the Mann-Whitney U test for non-parametric data and the χ^2 test.

Serum testosterone, sex hormone binding globulin, and corrected testosterone concentrations were similar in the three groups (table). Serum luteinising hormone concentration was significantly higher in group 1 than in group 2 ($p<0.01$). Ten of the 20 patients in group 1 had luteinising hormone concentrations above 10 IU/l compared with three of the 20 controls ($p<0.02$) and none of the patients in group 2 ($p<0.01$). Serum follicle stimulating hormone concentration was significantly higher in group 1 than group 2 ($p<0.05$). Follicle stimulating hormone concentration was above 10 IU/l in eight of the 20 patients in group 1 compared with three of the 20 controls ($p<0.02$) but in none of the patients in group 2. Similar differences were observed when patients and controls under the age of 70 were considered separately.

Comment

Serum concentrations of luteinising hormone and follicle stimulating hormone were significantly higher in men with peripheral vascular disease who were impotent than in men with peripheral vascular disease who had normal sexual activity and in controls. There was no difference in the concentration of testosterone and sex hormone binding globulin between the normal controls and either group of men with peripheral vascular disease, or in the concentrations of gonadotrophins between normal subjects and the men with peripheral vascular disease and normal sexual function. Confining the analysis to those aged less than 70 did not alter the results. Raised luteinising hormone and follicle stimulating hormone concentrations in the impotent patients were similar to those found in controls aged over 70.

These data suggest that a state of compensated hypogonadism may exist in men with peripheral vascular disease who are impotent. The increases in the concentrations of luteinising and follicle stimulating hormones were significant but the concentrations were only in the range associated with postmenopausal women (>10 IU/l) in 10 of the 20 patients, of whom six were aged under 70. The role of compensated hypogonadism in the pathogenesis of these patients' impotence is therefore uncertain and can be determined only by a trial of testosterone treatment. This would have to be conducted cautiously as the

Serum concentrations of testosterone, corrected testosterone, sex hormone binding globulin, luteinising hormone, and follicle stimulating hormone in patients with peripheral vascular disease and controls

	Patients with peripheral vascular disease			Controls
	All	Group 1 (impotent)	Group 2 (not impotent)	
No in group	32	20	12	20
Age (range) (years)	67 (38-79)	68 (38-79)	65 (48-78)	69 (39-79)
No with diabetes	7	4	3	
No with hypertension	19	11	8	
Median (range) ankle-brachial pressure index	0.64 (0.5-0.8)	0.63 (0.5-0.8)	0.66 (0.55-0.75)	
Median (range) total testosterone (nmol/l)	17.4 (10.1-30.0)	19 (10.1-30.0)	17.1 (12.0-21.9)	18.3 (10.3-38.1)
Median (range) sex hormone binding globulin (nmol/l)	41 (13-73)	47 (13-73)	32 (14-58)	44 (16-89)
Median (range) corrected testosterone† (nmol/l)	12.0 (7.0-25.7)	11.9 (7.0-25.6)	12.2 (7.7-25.7)	15.2 (6.1-30.0)
Median (range) luteinising hormone (IU/l)	7.9 (2.2-50.0)	9.9** (5.5-50.0)	5.7 (2.2-8.3)	5.7 (2.7-18.2)
Median (range) follicle stimulating hormone (IU/l)	5.9 (0.9-20.0)	7.6* (2.0-20.0)	4.5 (0.9-7.8)	5.0 (1.1-13.6)

* $p<0.05$ and † $p<0.002$ compared with group 2. ** $p<0.01$ compared with controls.

†Corrected to sex hormone binding globulin concentration of 30 nmol/l.