Antibody persistence in stored sera—On testing in 1978 the geometric mean titre of haemagglutination inhibition antibody in the 16 sera collected 46 days after vaccination and still available for retitration was 64·4, compared with 128·8 originally; five samples (31%) showed a fourfold fall in titre (table). This was probably due to loss of antibody during storage and not to the different methods of removing non-specific inhibitors (acid-washed kaolin in 1968, manganous chloride and heparin in 1978).

Antibody persistence after vaccination—All sera had detectable haemagglutination antibody 10 years after vaccination (table). Antibody titres had fallen fourfold in four (20%) subjects (three of the 12 not revaccinated and one of the eight revaccinated) and had increased fourfold in one of the revaccinated subjects. Neutralising antibody was present in all 12 subjects not revaccinated, at titres of 1 in 32 (three subjects), 1 in 8 (five), and 1 in 4 (four).

Titres of haemagglutination inhibition antibody in sera collected 46 days after vaccination in 1968 (tested in 1968 and 1978) and 10 years after vaccination. (Subjects in cases 13-20 were revaccinated between 1970 and 1978)

Case No	Sera obtained 46 days after vaccination*		1978 sera*
	1968	1978	
1	320	320	80
2	160	80†	20
3	160	80	40
4	320	80†	40
5	40	40	40
6	160	40	20
7	160	80	40
8	160	160	80
9	160	80	20
10	40	40	20
11	320	80	80
12	160	20‡	20
13	160	80	40
14	40	160†	40
15	160	40	20
16	320	80	160
17	80	20	80
18	80	40	40
19	160	80	80
20	40	40	40
Geometric mean titre	129·9	65·0	41·4

*Titrated in parallel.
In four cases sera obtained in 1968 were no longer available, so †sera obtained in 1970 and ‡sera obtained in 1974 were substituted.

Comment

The duration of immunity elicited by a single dose of rubella vaccine is still a major issue. Our results show that haemagglutination inhibition and neutralising serum antibodies were present in all subjects 10 years after vaccination with the Wistar RA27/3 strain, but titres in several subjects were low and there might be cause for concern if they fell further. In sera collected soon after vaccination, loss of antibody with storage may cause the extent to which antibody has waned to be underestimated when these and recently collected sera are titrated in parallel.

The peak childbearing age is 29 in the Irish Republic and 26 in England and Wales. Thus if revaccination of women is to be avoided vaccine administered at about the age of 12 should elicit immunity for at least three decades. Clearly, better definition of these issues is needed, including a follow-up of further groups of subjects vaccinated for 10 years or more.

1 Balfour HH, Amren DP. Rubella, measles and mumps antibodies following vaccination of children. *Am J Dis Child* 1978;**132**:573-7.
2 Best JM, Harcourt GC, O'Shea S, Banatuala JE. Rubella vaccine. *Lancet* 1979;ii:690-1.
3 Hillary IB, Meenan PN, Griffith AH, Draper CC, Laurence GD. Rubella vaccine trial in children. *Br Med J* 1969;ii:531-2.
4 Hillary IB. Persistence of antibody after subcutaneous vaccination with Wistar RA27/3 rubella vaccine. *J Hyg (Camb)* 1971;**69**:369-72.
5 Hillary IB, Freestone DS. Persistence of antibody induced by rubella vaccine (Wistar RA27/3 strain) after six years. *J Hyg (Camb)* 1975;**75**:407-11.

(*Accepted 24 March 1980*)

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Prostacyclin in pregnancy

Stable prostaglandins have physiological roles in pregnancy, but the recently discovered unstable eicosanoids thromboxane A_2, prostacyclin (PGI_2), and the leukotrienes[1] have not been studied in pregnant women. Using a new gas chromatography-mass spectrometry assay[2] we have measured the stable hydration product of PGI_2, 6-oxo-$PGF_{1\alpha}$, in the plasma of pregnant women. Platelet aggregability was also measured.

Patients, methods, and results

Five groups were studied: 18 non-pregnant women, eight women taking oral contraceptives, six women in early pregnancy (8 to 15 weeks), nine women in late pregnancy (28 to 39 weeks), and seven women one to seven days after delivery. No patient had taken aspirin-like drugs within seven days of the study. The outcome of all the pregnancies was normal.

Blood was drawn without stasis and the heparinised blood rapidly centrifuged at 4°C in the presence of indomethacin 0·01 mmol/l. Plasma 6-oxo-$PGF_{1\alpha}$ was assayed by gas chromatography-mass spectrometry.[2] The lower limit of sensitivity was 62·5 pg/ml. The coefficient of variation at this concentration was 11%. A further blood sample was citrated and platelet-rich plasma obtained within one minute using ultracentrifugation (Eppendorf). The minimum dose of adenosine diphosphate (ADP) causing irreversible platelet aggregation was determined (Payton aggregometer).

The plasma 6-oxo-$PGF_{1\alpha}$ concentrations were similar in all patients except in late pregnancy and the puerperium, when the levels were almost double those in non-pregnant women (table). Women in late pregnancy and the puerperium also had significantly more aggregable platelets. The mean concentration of 6-oxo-$PGF_{1\alpha}$ in non-pregnant women was similar to that in healthy men of similar age.

Mean (±SD) plasma concentrations of 6-oxo-$PGF_{1\alpha}$ and platelet aggregability in five groups of patients

Patient group	No	Plasma 6-oxo-$PGF_{1\alpha}$ (pg/ml)	Minimum ADP concentration for irreversible aggregation (μmol/l)
Non-pregnant	18	123±22	2·07±0·78
Non-pregnant on oral contraceptives	8	138±26	2·65±0·71
Early pregnancy (<12 weeks)	6	131±17	2·06±0·45
Late pregnancy (>28 weeks)	9	244±133*	0·58±0·54*
Puerperium (<7 days after delivery)	7	227±108*	0·61±0·48*

*Significant difference from mean value in non-pregnant women ($p < 0·001$, Students t test).
ADP = Adenosine diphosphate.

Comment

We have shown a high concentration of plasma 6-oxo-$PGF_{1\alpha}$ in late pregnancy. The concentration of 6-oxo-$PGF_{1\alpha}$ measured in plasma in vitro probably reflects the circulating concentration of active prostacyclin. Prostacyclin is unstable and hydrolyses to 6-oxo-$PGF_{1\alpha}$ during extraction. In previous experiments we have shown a parallelism between concentrations of this hydration product and expected changes in circulating prostacyclin. Prostacyclin is a circulating hormone with a potent platelet inhibitor action. A balance probably exists between proaggregatory thromboxane production in platelets and anti-aggregatory prostacyclin production by vascular endothelium.[1] Our results show that this balance is disturbed in late pregnancy since prostacyclin concentrations are high but the platelets are hyper-aggregable. The platelet results accord with the clinical experience that thromboembolism is more common in women at this time. The source of the increase in prostacyclin is not known. The main source of circulating prostacyclin in non-pregnant adults is the pulmonary circulation.[3] During pregnancy the placenta and uterus might each contribute prostacyclin since both generate prostacyclin in vitro.[4] High concentrations of 6-oxo-$PGF_{1\alpha}$ have been detected in human amniotic fluid. Human umbilical blood vessels are more active in synthesising PGI_2 than are adult blood vessels[5] so that the fetus might be a source, but the high concentration of 6-oxo-$PGF_{1\alpha}$ post partum makes this less likely.

What role might prostacyclin have in pregnancy? It might be concerned in the characteristic vasodilatation. Increased prostacyclin production might be an adaptive response to a primary increase in platelet aggregability. Platelet consumption is an early feature in pre-eclampsia and a major component of disseminated intravascular coagulation, a serious complication of late pregnancy. In these

conditions the balance between thromboxane and prostacyclin may be tipped more strongly in the direction of aggregation. Interestingly, the incidence of pre-eclampsia in women exposed to aspirin during pregnancy is lower since aspirin in low doses irreversibly inhibits platelet cyclo-oxygenase, the source of thromboxane A_2. It is an exciting possibility that a relative deficiency of prostacyclin might be a factor in the pathogenesis of pre-eclampsia.

We are grateful to Action Research, the Wellcome Trust, and the Cilag Chemie Foundation.

[1] Moncada S, Vane JR. Pharmacology and endogenous roles of prostaglandin endoperoxides, thromboxane A_2 and prostacyclin. *Pharmacol Rev* 1979; **30**:293-331.
[2] Hensby CN, FitzGerald G, Friedman LA, Lewis PJ, Dollery CT. Measurement of 6-oxo-$PGF_{1\alpha}$ in human plasma using gas chromatography-mass spectrometry. *Prostaglandins* 1979;**18**:731-6.
[3] Hensby CN, Barnes PJ, Dollery CT, Dargie H. Production of 6-oxo-$PGF_{1\alpha}$ by human lung in vivo. *Lancet* 1979;ii:1162-3.
[4] Omini C, Folco GC, Pasargiklian R, Fano M, Berti F. Prostacyclin (PGI_2) in pregnant human uterus. *Prostaglandins* 1979;**17**:113-20.
[5] Remuzzi G, Misiani R, Muratore D, *et al.* Prostacyclin and human fetal circulation. *Prostaglandins* 1979;**18**:341-8.

(*Accepted 18 March 1980*)

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Hypertension after taking hydrallazine

Hydrallazine is a potent hypotensive drug with well-recognised side effects.[1] We report a case in which the patient had a paradoxical rise of blood pressure after taking hydrallazine. This has not been reported.

Case report

An 18-year-old woman was admitted with a 15-month history of symptomless hypertension discovered at routine medical examination, for which she was taking propranolol 80 mg thrice daily and bendrofluazide 10 mg each morning. She was not taking oral contraceptives. There was no relevant past or family history. Clinical examination, including fundoscopy, was normal except for grade 1/4 left ventricular hypertrophy. Her blood pressure was 180/110 mm Hg supine. The results of analysis and microscopy of the urine were normal, creatinine clearance was 85 ml/min, and urinary vanillylmandlic acid was within normal limits. Although intravenous pyelography was normal, isotope renography showed a reduced vascular peak on the right. Hydrallazine by mouth was added to her treatment. One hour after the first dose she developed headache, tachycardia (150/min), and her supine blood pressure rose to 180/140 mm Hg. A further intramuscular dose of 20 mg hydrallazine was given and within 15 minutes her headache had worsened, her vision became blurred, and the supine blood pressure rose to 240/160. Her pulse rate did not alter further and the fundi were unchanged. Her blood pressure was controlled by diazoxide 150 mg in a single intravenous dose. The diastolic pressure remained below 100 mm Hg for the next 12 hours, the pulse rate falling to 80/min.

The patient was subsequently given a further dose of hydrallazine 50 mg by mouth. Headache, nausea, and tachycardia (150/min) recurred and her supine blood pressure rose to 190/140 mm Hg within an hour. It fell spontaneously to normal over the next four hours. The dose of propranolol was subsequently increased to 120 mg thrice daily and her diastolic blood pressure remained below 90 mm Hg. She remained taking propranolol 120 mg thrice daily and bendrofluazide 10 mg each morning throughout further investigation. Her peripheral plasma renin activity at that time was within the normal range and showed a normal response to posture. A percutaneous femoral arteriogram showed that her right renal artery was stenosed just beyond its origin. The upper pole of the right kidney was supplied by tortuous collaterals originating from the base of the renal artery and the lower pole supplied by tortuous and enlarged lumbar vessels. The left renal artery was normal. Autotransplantation of the right kidney with reconstruction of the stenosed right renal artery was performed. Her blood pressure over two years has remained normal without treatment. Histology of the renal artery showed fibromuscular hyperplasia.

Comment

The response to surgery shows that this patient's hypertension was due to the renal artery stenosis. The mechanism for the paradoxical hypertension remains unclear. Increase in flow across an obstruction increases the pressure gradient across that obstruction. An increase in renal blood flow due to hydrallazine-induced vasodilation will therefore drop the perfusion pressure distal to the obstruction and may cause hyperreninaemia. Plasma renin activity was not measured during the period of paroxysmal hypertension but normal renin activities were recorded when the diastolic blood pressure was persistently above 105 mm Hg. Renin activity also showed a normal increase on upright posture despite the coexistent beta-blockade. This suggests that the effect of the propranolol on plasma renin activity was small and low perfusion pressure distal to the stenosis was not causing hyperreninaemia. Reflex tachycardia is an accompaniment of vasodilator treatment. This reflex is interrupted by beta-blockade. The pronounced tachycardia noted in our patient suggests that this reflex still existed. But it fails to explain the rise in blood pressure unless increased catecholamine release also caused a rise in peripheral resistance in excess of an initial fall in resistance caused by hydrallazine.

The relation of the hypertensive response to this patient's renal artery stenosis remains conjectural. The response, however, is dangerous and should be remembered when hydrallazine and possibly other vasodilators are ineffective, particularly in association with renovascular hypertension.

We thank Professor A W Asscher for permission to report this case and Dr A J Wilton for renin assays.

[1] Nickerson M, Ruedy J. Antihypertensive agents and the drug therapy of hypertension. In: LS Goodman, A Gilman, eds. *The pharmacological basis of therapeutics*. New York: MacMillan, 1975:705-7.

(*Accepted 18 March 1980*)

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ONE HUNDRED YEARS AGO The following translation of a Chinese placard regarding the highly immoral practice of consuming cow's milk is quoted by *Nature* from the *Foochow Herald*. "Strictly refrain from eating cow's milk! Man should not rob the beasts of their food. Moreover, of all beasts the cow is the most useful and meritorious. Men who do not discriminate between mankind and beasts are worse than senseless. Those who sell milk darken their consciences for gain, and those who eat cow's milk foolishly think they are benefiting their bodies. Men who take medicine should first carefully investigate and find out its nature. Why do not those who eat cow's milk consider and inquire into its origin? For instance, men beget children, and while the children are small they depend upon the milk for their nourishment: so it is also with beasts. But when men buy milk to eat, do they not do injury to the life of the calf? And is there not bitter hatred and distress in the minds of both cow and calf? Beasts cannot speak: how, then, are they able to tell the man that, in eating the milk of beasts, his body becomes like that of birds and beasts? But if men wish to take strengthening medicine, there are numberless other articles in the world that are beneficial. What necessity, then, is there for taking cow's milk? Besides this, the death and life of men have their fixed number and limit, and this cow's milk cannot lengthen out and continue the life of man. Since, then, all know the truth, that it cannot do this, all ought to act with loving and benevolent spirit: especially all who receive this exhortation should keep from eating milk. The children of those who cause their families to refrain from eating milk will be preserved to grow up: they also will thus lengthen out their own lives, and will escape from evil in time of fatal epidemics. If such persons be able also to exhort others, who are ignorant of the first principles, to leave off the eating of milk, their descendants shall surely prosper. Published by the Hall of Good Exhortations. The xylographic blocks are deposited in the Ung Ling Kóh." (*British Medical Journal*, 1880.)