

Hypertension and arterial development

Long-term considerations

C. L. BERRY

From the Department of Morbid Anatomy, The London Hospital, London

SUMMARY A considerable body of evidence supports the view that haemodynamic factors, acting during growth and development, affect the ultimate form of the larger arteries. Many of the changes induced in vessels by high pressure or flow are adaptive and effectively minimise alterations in vessel function, but these changes may predispose to degenerative disease. 'Early intervention' in arterial disease implies intervention in the first and second decades of life.

In a lecture to the Royal Society of Medicine, Morris (1973) pointed out that, 'too much of medical care is absorbed in advanced disease, in rescue, reprieve, patching up and lost causes, marginal benefits and diminishing returns'. The value of preventive measures in vascular disease is evident when we consider that the number of hospital days 'consumed' each year by cerebrovascular disease alone is around 10 000 000 and rising.

Hypertension plays a central role in the genesis of arterial disease. Blood pressure rises with age in man; screening surveys in England and Scotland have suggested that around 40 per cent of men will have casual diastolic pressures above 90 mmHg in middle age, a level that is associated with a significant increase in risk of cardiovascular death, non-fatal stroke, and myocardial infarction (*Journal of the Royal College of Physicians of London*, 1976). If there are 2.5 million people in the United Kingdom with hypertension as Fry (1974) suggests, the problem is a massive one. It is unfortunately true that the detection of hypertension in adults may not result in active intervention or an alteration in the natural history of the disease. In pointing out the drawbacks to screening for high blood pressure, Sackett (1974) has described how physicians in the community may not initiate treatment when hypertension is discovered and symptom-free hypertensives may not continue treatment if it is initiated. Though the critical effect of blood pressure on cerebrovascular disease is well established, and the way in which lowering the blood pressure is

associated with decreased morbidity and mortality is well documented (*Journal of the American Medical Association*, 1967, 1970), the value of such control in coronary heart disease is not. This is in spite of epidemiological, pathological, experimental, and clinical evidence that hypertension accelerates the development of atherosclerosis, itself the most important causal factor in coronary heart disease. In a recent study on risk factors for coronary heart disease Reid *et al.* (1976) surveyed 18 403 British civil servants, their findings confirming the importance of hypertension in its genesis. They state 'as blood-pressure, whether systolic or diastolic, rises, so does the risk of death from C.H.D.'. Meade and Chakrabarti (1972) have suggested that this difference between the effects of hypotensive therapy on coronary heart disease and cerebrovascular disease indicates that earlier intervention may be necessary if a positive result is to be anticipated in coronary heart disease. Certainly hypotensive therapy has its dangers when blood flow is diminished in pathologically altered vessels (Jackson *et al.*, 1976).

These findings suggest a need to intervene earlier in the natural history of hypertension. The benefits conferred in the prevention of atherosclerotic vascular disease might be greater than those conferred by changes in diet, since Whyte (1975) has found from an analysis of the Framingham data that lowering plasma cholesterol from 310 to 260 mg/100 ml (8.03 to 6.73 mmol/l) starting at 35 years of age would benefit only 6 in 100 non-smokers in terms of prevention of coronary incidents. It is likely that antihypertensive therapy would need to begin very early in life to be effective. Is there any justification for such a step?

Blood pressures in children

The studies of Graham *et al.* (1945) established 'normal' blood pressure levels for children, and showed that 3 to 4 per cent of children have blood pressures more than 2 SD above the mean. Londe's observations (1966, 1968) extended those of Graham. Later work was more concerned with the hypertensive group. In 1971, Londe *et al.* reported a study of a group of 74 young patients with high blood pressure (followed for at least a year). Seventeen of the 74 patients had developed hypertension under 6 years of age, all but 2 were below 15 years. In only 5 children was a cause for the hypertension found, but the prevalence of obesity and parental hypertension was noted to be significantly higher in the hypertensive children than in normotensive controls. Of the 74 hypertensive children, 53 were overweight; of 54 hypertensive children for whom an adequate family history was available, 24 had one parent with hypertension, whereas this was true of only 9 of 50 controls. A high prevalence of obesity and parental hypertension in children with raised blood pressure was originally observed by Hahn (1952) and has been frequently recorded since then.

Zinner *et al.* (1971) also showed a familial influence on blood pressure in childhood and suggested that a familial tendency to hypertension can be noted early in life. In a family study Beresford and Holland (1973) observed a correlation between blood pressure and weight; they also found that parental blood pressure had an important effect in determining the blood pressure of the offspring after correction for the effects of height and weight. The authors concluded that by the age of 6 the blood pressure level of the child is already related to the levels of the parents. Buck (1973) also suggested that if blood pressure is raised at the age of 5 it is likely to remain high for some years. Important recent observations by de Swiet *et al.* (1976) suggest that blood pressure levels in individuals are determined very early indeed, systolic blood pressure at 4 to 6 days of age being significantly related to pressure at 5 to 7 weeks.

For many years it was considered that there was no real racial difference in blood pressure levels in children. The studies of Rose (1962) and Dube *et al.* (1975) suggested that levels were comparable despite the high prevalence of essential hypertension and related disorders in adult black populations (Finnerty, 1971; Chenoweth, 1973). However, in the Bogalusa Heart study (Voors *et al.*, 1976), an investigation of the natural history of hypertension between 5 and 14 years, black children were found to have higher blood pressures than whites, a

difference not accounted for by arm size differences, and evident before the age of ten. When the distribution of blood pressures was studied it was notable that the difference between black and white children was most marked at the 95th centile where χ^2 tests confirmed the significance of the difference. Children in the upper 5 per cent of the pressure ranks were most affected.

These various observations provide an increasing body of evidence which suggests that blood pressure levels in individuals are partly genetically determined, and are set early in life, at a time when blood vessels are growing and developing. Individuals with higher blood pressures might develop vessels with a structure that predisposes to degenerative change. Can this suggestion be supported?

Vessel structure and blood pressure

There is a considerable body of evidence which suggests that interference with development of an organ or tissue at an early stage may permanently affect function and form. This principle has been established in the central nervous system (Dobbing and Sands, 1970; Dobbing, 1970), the immunoreactive tissues (Smythe *et al.*, 1971; Edelman *et al.*, 1973), the fat organ (Brook, 1972; Salans *et al.*, 1973), and the skeleton, where Garn *et al.* (1967) and Newton-John and Morgan (1968) have suggested that the best natural protection against the sequelae of bone loss in later life is the development of a large skeletal mass during childhood, a suggestion supported by the findings of Gryfe *et al.* (1971). Perhaps, in a similar way, blood vessel structure is determined for later life by haemodynamic stress during growth.

Change in blood pressure certainly alters the form of the larger arteries in man. Earlier morphological studies of human arteries during ageing (Wright, 1963; Dible, 1964) emphasised that vessels may respond to haemodynamic changes by change in structure until relatively late in life and show that degenerative changes occur commonly from the early part of the third decade. More recent studies show that alteration in vessel form is more readily produced in early life; banding of the pulmonary artery in patients with high pulmonary blood flow produces a very different wall thickness proximal and distal to the band within 10 days of operation (Berry, 1969; Stark *et al.*, 1972; and see Fig. 1). Changes in aortic haemodynamics at birth are probably responsible for the rapid increase in elastin production in the wall of the aorta in human neonates (Berry *et al.*, 1972) and for a considerable fall in the relative wall thickness, a change partly caused by the increase in aortic size in early life.

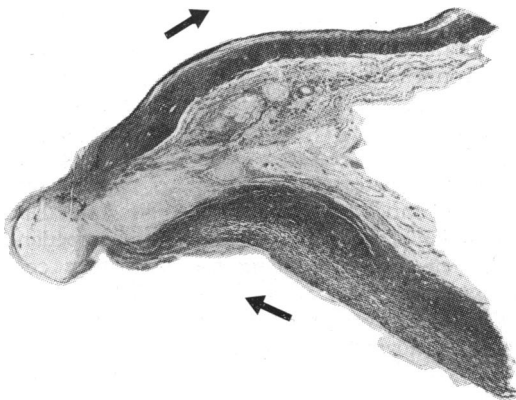


Fig. 1 Longitudinal section. Pig pulmonary artery after experimental banding. Arrows indicate the direction of blood flow. Note difference in medial thickness on the high pressure side of the band. (Elastic Van Gieson $\times 5.5$)

The aorta increases from a diameter of 12 mm at a body surface area of 0.30 m² to 25 mm at a body surface area of 1.70 m² and a variation of little more than 2 mm covers the 5 to 95 centile range (Epstein *et al.*, 1975). This change alone will alter mechanical stress in the wall in a well-defined way. At a constant pressure the tangential tension in a vessel wall of finite thickness is given by the Lamé approximation:

$$T = P \frac{r}{h} \quad (1)$$

where T is the tangential tension, P is the blood pressure, r the mid-wall radius, and h the wall

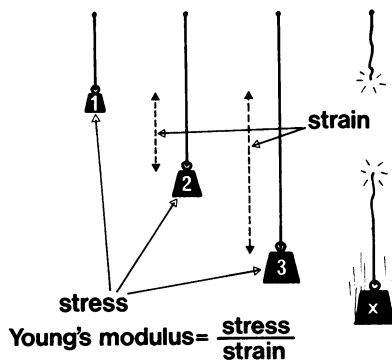


Fig. 2 Diagrammatic representation of stress and strain shown for a material obeying Hooke's law, for example steel wire. Hooke's law states that the extension of a material is proportional to the load applied. Strain is customarily considered to be the ratio of the extension in length to the original length.

thickness. Thus as r rises, T will rise. In fact, as we have seen, P also rises with age and h falls (see below).

What factors are important in the response of vessel walls to these changes in load?

It is useful to consider the stresses and strains in vessels, but these terms should be used accurately. In Fig. 2 a diagrammatic representation of stress (force/unit area) and strain, here shown as the proportional elongation of a wire, is presented. Young's modulus is calculated by dividing stress by strain. The mechanical properties of the vessel wall will determine the change in radius (strain) for a given pressure increment (stress). The ratio of

change in radius to a given radius $\frac{\Delta r}{r}$ is the *incremental strain*, the pressure increment over which this

change occurs (Δp) should be specified for each series of measurements. Thus for a 10 mmHg

increment in pressure a change in $\frac{\Delta r}{r}$ will occur, but a

further 10 mmHg increment will not necessarily produce the same effect in materials which do not obey Hooke's law. Redefining tangential tension as *stress* (that is force/unit area) we may then calculate an elastic modulus (y) for an artery from the simple formula:

$$y \doteq 0.75 \times \frac{\text{Stress}}{\text{Strain}} \quad (2)$$

The figure 0.75 is a constant, included since the mechanical properties of an artery are not constant in all directions; vessels *in situ* elongate very little until high pressures (> 300 mmHg) are reached.

Young's modulus is not constant for arteries over a wide range of stresses as it is for steel wire. In

elastic vessels the ratio $\frac{\text{stress}}{\text{strain}}$ increases with applied

stress; that is, the vessel becomes functionally stiffer at higher pressures. It is for this reason that we have measured incremental strains so that changes over a wide range of radius can be considered and vessels of different size compared (for fuller discussion, see Berry *et al.*, 1975).

The endothelium contributes little to the mechanical properties of the aortic wall (Burton, 1954) and muscle is similarly of little mechanical importance (Berry *et al.*, 1975). The principal contribution is made by the scleroproteins, collagen and elastin, which act in combination as a 'two-phase' material (like glass reinforced plastic). Initially, the vessel radius increases rapidly with small pressure increments, subsequently the vessel becomes less distensible, and at pressures around

twice the mean systolic level little change in radius occurs for each pressure increment.

At low pressures (< 75 mmHg) the elastic arteries apparently behave as a tube of pure elastin. Above these levels decrease in strain (increased stiffness) presumably reflects an increased recruitment of collagen. Measurements at high pressures (> 200 mmHg) are not sufficiently accurate to permit anything but estimates of vessel wall stiffness at these levels; however, it is evident from the very small incremental change in radius that the wall is very stiff and that its mechanical properties approximate to those of collagen.

Relative wall thickness (h/r) decreases towards a constant value with increasing pressure; the magnitude of this change is greater than that which occurs during early life as the vessel wall continues to develop postnatally, but is of the same order. This will, of course, affect strain values by a simple geometric effect (on radius). Because of this effect, though the incremental elastic modulus does not differ in the thoracic and abdominal aorta, measured strain values in the abdominal part of the vessel are less (i.e. the vessel is stiffer) because of the greater wall thickness. It seems from our earlier studies that the difference in proportion of collagen and elastin in the two segments of the aorta are of lesser importance than geometrical differences in determining the mechanical properties of this part of the wall. Incremental elastic modulus changes little with age, supporting the suggestion that the increase in strain values seen in the first 10 weeks of life is largely caused by the decrease in relative wall thickness in this period.

Changes in hypertension

In a study of rats made hypertensive (Berry and Greenwald, 1976), animals hypertensive for 6 weeks during growth were compared with animals hypertensive until death (around 20 to 24 weeks) and with normal animals. The vessel walls of hypertensive rats became thickened, as many authors have found, the relative wall thickness (h/r) increasing rapidly, but falling rapidly when hypertension was relieved. However, this change is not entirely reversible; in animals hypertensive from 4 to 10 weeks, values of h/r were still abnormally high at a year. The functional changes that accompanied these findings were equally striking. Incremental strain, a measurement of the functional stiffness of a vessel, at any particular pressure was different in hypertensive and normotensive animals. At a pressure of 100 mmHg, hypertensive vessels were *more* distensible than normotensive, but at the effective systolic pressure of each group of hypertensive animals the

aorta showed an incremental strain which was lower than normal but tended towards normal values as the duration of hypertension increased, a finding since confirmed by R. Cox (1977, personal communication). This progressive increase in strain in hypertensive vessels suggests that an adaptive response occurs tending to maintain a strain value that approximates to normal. This may preserve the differential between the high impedance termination of the arterial tree and its low impedance origin, effectively reducing the oscillatory component of the cardiac work (Taylor, 1964).

This tendency to preserve normal arterial function has morphological consequences which are complex. If one assumes no change in the physicochemical arrangements of the components of the wall, increase in wall thickness alone will result in a *decrease* in strain (increased functional stiffness). However, because of the non-linearity of the response of the wall to distension (Fig. 3), an increase in wall thickness will result in a smaller total distension for a given pressure and thus *increase* strain (decreased functional stiffness), because the artery is now lower down the slope in Fig. 3. The detailed interactions are discussed elsewhere (Berry and Greenwald, 1976), but one may conclude that dimensional changes alone will not account for the functional differences observed.

It is remarkable how effective the adaptive arterial response is. If incremental strain values are compared at a given degree of distension hypertensive animals have a value one-fifth normal in the early stages of hypertension. This difference is not maintained; by 20 weeks average values are about

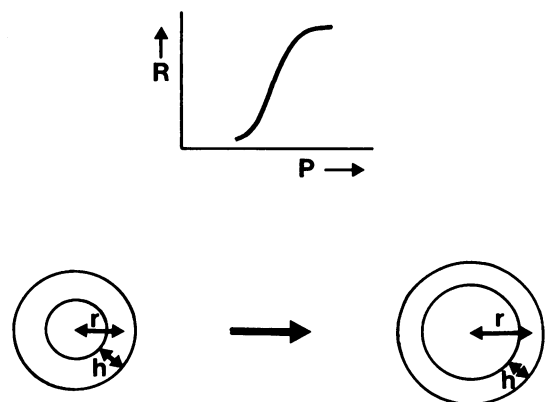


Fig. 3 Change in wall thickness in an artery during distension. Changes in wall thickness will, in effect, alter the position of the vessel on the curve. R is mid-wall radius, P pressure.

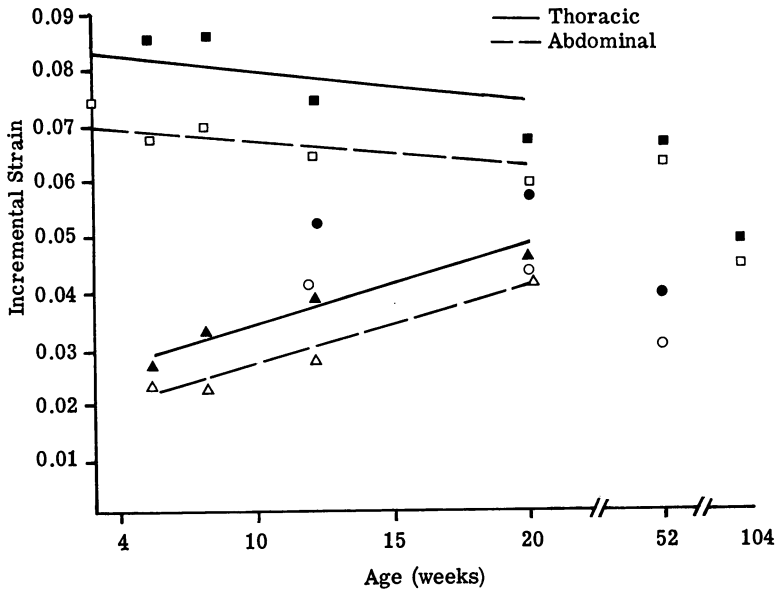


Fig. 4 Variation of incremental strain with age in normal ■ □, hypertensive ▲ △, and previously hypertensive animals ● ○. Open symbols abdominal, solid thoracic, aortic segment. (Reproduced from Cardiovascular Research, 10, 1976, p. 441.)

half normal (Fig. 4). This sequence of events shows a progressive reduction in the stiffness of the hypertensive vessel. This desirable physiological event may have pathological consequences.

Clinical correlation

Is there any evidence that adaptive changes of this type occur in man? In the single umbilical artery syndrome, the circulation during intrauterine growth and development is as shown in Fig. 5. A great proportion of the blood flow and the entire flow to the placenta runs through only one common iliac artery. It is likely that such haemodynamic variation will produce changes in vessel wall structure, and so we arranged to measure arterial distensibility in a group of children (5 to 9 years) who had been studied by Bryan and Kohler (1974), who were known to have had a single umbilical artery at birth. A non-invasive Doppler technique was used to measure pulse wave velocity, directly related to wall stiffness, and showed that there was a great difference in vessel wall behaviour on the two sides, which was still demonstrable at 9 years of age. The children were normal in all other respects (see Bryan and Kohler) and had no leg shortening. Yet the compliance of the arterial segment between the aortic bifurcation and the femoral ligament was greatly increased on the side from which the single umbilical artery had arisen in the children examined (Fig. 6). Leg artery compliances did not differ significantly on the two sides (Berry *et al.*, 1976).

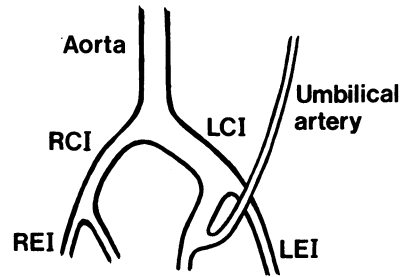


Fig. 5 Diagram of vasculature in the single umbilical artery syndrome. Common iliac arteries RCI, LCI, external iliac arteries REI, LEI.

Since there is pulsatile flow in this system, and if we assume that the common iliac artery from which the umbilical artery originates has to accommodate approximately twice the volume flow, this could be accomplished by doubling the volume strain $\frac{\Delta V}{V}$ (i.e. the compliance).

From our figures the most compliant iliac arterial segment has a compliance 1.9 times that of the aorta. As we have shown that the elastic properties of the components of the aortic wall do not change with age (Berry *et al.*, 1975), the change is probably brought about by altering the ratio of vessel radius to wall thickness. Morphological changes illustrated by Meyer and Lind (1974) suggest that this is what happens, and the change in wall structure in a

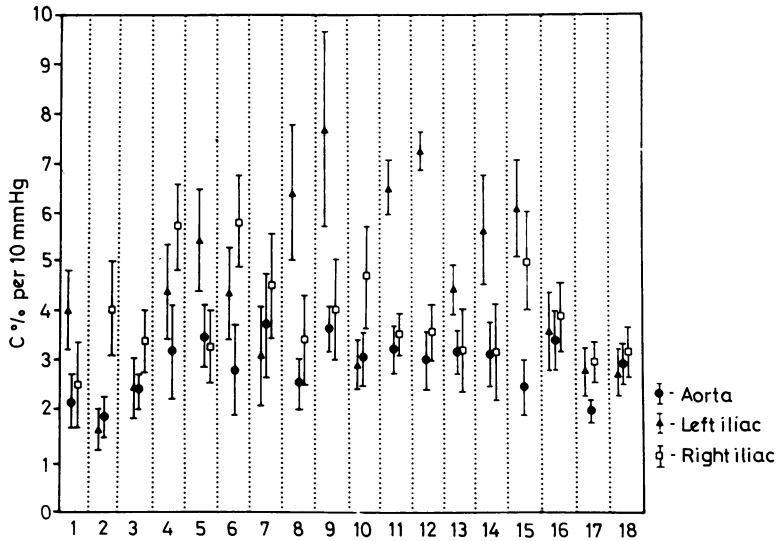


Fig. 6 Compliance of aortic and iliac pathways in 18 subjects with single umbilical artery. (Reproduced from *British Heart Journal*, 38, 1976, p. 514.)

personally observed case (see Fig. 7 a-f) where a small muscular artery was found on the side of the missing umbilical artery and a large elastic vessel on the other, confirms a major change in r/h.

Pathological consequences

These changes in arterial form may be disadvantageous in several ways. In functional terms Gosling and King (1975) have suggested that the initial event in atheroma is a departure of large artery compliance from 'in health' values. In the children with single umbilical artery studied by Meyer and Lind, atherosclerosis was found in the larger iliac vessels of two cases dying at 18 months and 4 years of age, much earlier than has been reported previously, suggesting that atypical arterial wall structure may predispose to degenerative disease. It seems probable that minor changes in wall thickness, induced by hypertension, will be found in children in the upper ranges of blood pressure centiles. We are now studying vessel wall function in a group of children with known blood pressure histories (Greenwald *et al.*, 1978, in press).

Apart from functional changes which resemble accelerated ageing, hypertension has other documented ill effects. Pressure changes induce rapid smooth muscle cell division in elastic arteries in experimental hypertension (Bevan, 1976). Since the smooth muscle cell synthesises aortic scleroproteins (Ross, 1971; Ross and Klebanoff, 1971), this cell multiplication appears to be the initial step in the response of the wall to stress. It has been

established for human pulmonary arteries that the thickness of the lamellar units which make up the wall of elastic arteries is increased by this proliferation but their number is not (Haworth, 1976). Comparison of hypertensive animals with controls examined in a previous morphological study of the rat aorta throughout life suggests that this is also true for the systemic circulation. Such changes may disturb the blood supply of the inner media and increase the width of the hypoxic zone normally present. Lipid accumulation would be favoured by this and by the increased endothelial permeability demonstrable in hypertension. A role for lipids in atherogenesis is established and whatever its relative importance, it is related to proliferation of smooth muscle cells, thought in turn to be a 'key event' in atherosclerosis by Ross and Glomset (1973). Cause and effect are difficult to separate, but vessel variability may underly some of the human variability in susceptibility to degenerative vascular disease.

The mode of action of the stimuli producing the change in wall structure (pressure, flow, tension, etc.) is uncertain. Present preliminary experiments suggest that an applied strain across smooth muscle cells encourages cell division and converts them from the contractile to the synthetic (scleroprotein producing) phase. The way in which loads are distributed in the large elastic arteries is now being investigated; though the contribution of smooth muscle cells is negligible in mechanical terms (*see above*), they may be important in spacing the load-distributing and load-bearing scleroproteins they produce.

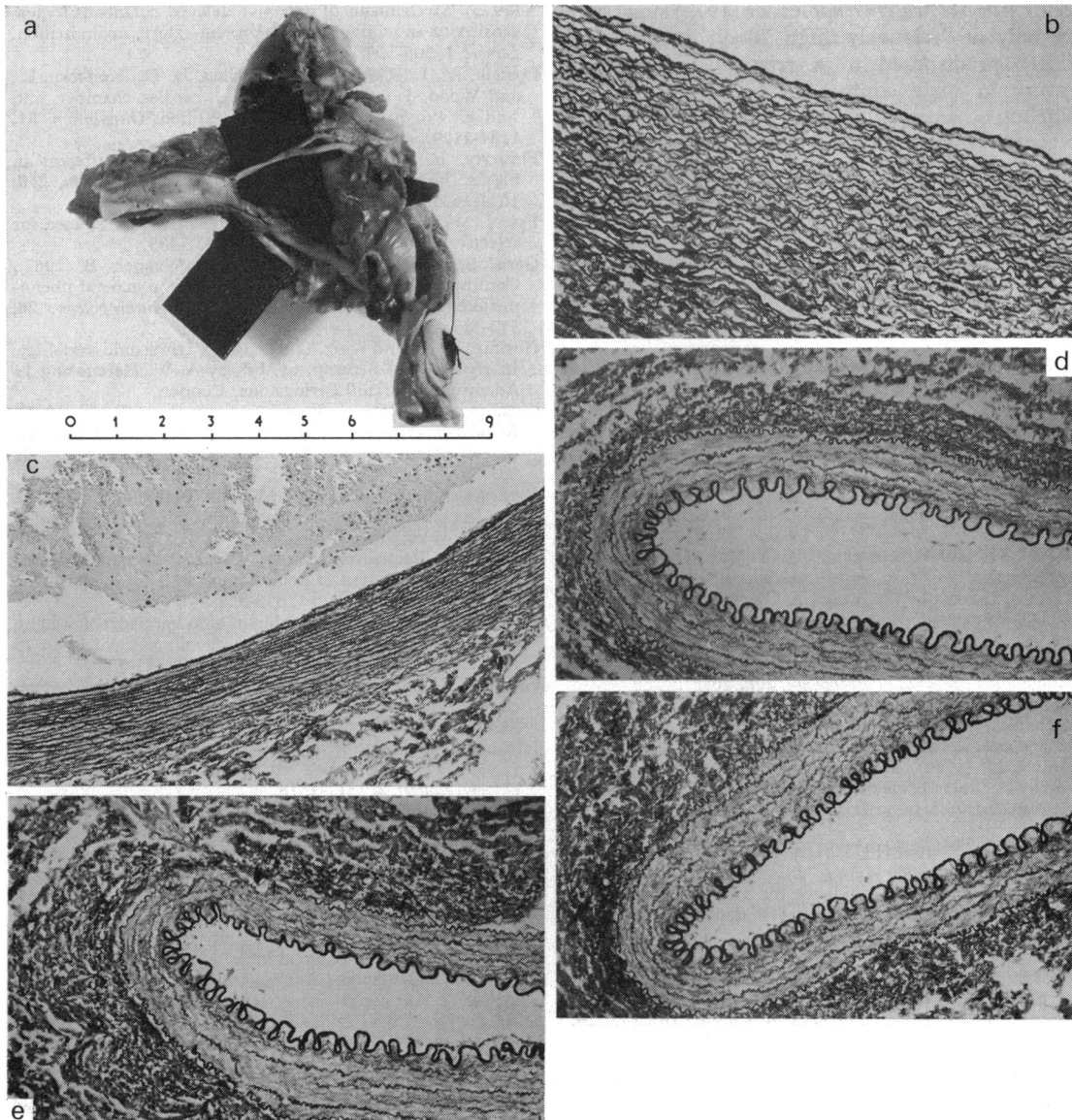


Fig. 7 (a) Gross specimen from child with a single umbilical artery. The aorta is to the left. The difference between left and right common iliac and internal iliac vessels is apparent. (b) Aorta above bifurcation. (Elastic Van Gieson $\times 67$.) (c) Right common iliac artery. Laminar elastic structure. (Elastic Van Gieson $\times 67$.) (d) Left common iliac artery. A muscular vessel. (Elastic Van Gieson $\times 110$.) (e) Right internal iliac artery. A muscular artery, normal for this site. (Elastic Van Gieson $\times 110$.) (f) Left internal iliac artery. Also a muscular vessel. (Elastic Van Gieson $\times 110$.)

If blood pressure levels are determined early in life, and higher levels induce irreversible changes in vessels, perhaps hypotensive therapy should also be started early. There is evidence, from the spontaneously hypertensive 'Okamoto' rats, that treatment with hypotensive drugs as a preventive measure limits the structural changes in the cardio-

vascular system and greatly diminishes the rise in blood pressure that occurs in these animals in later life (Weiss, 1974). Might the same be true for man? If it were, we could confidently expect an improvement in morbidity and mortality from vascular disease if blood pressure could be lowered in early life.

A *British Medical Journal* leader (1973) suggested that only if 'relatively high blood pressure in children predisposed to a relatively high blood pressure in early adult life would treatment in childhood be acceptable as a way of further reducing the complications of hypertension in later life', and concluded that 'the routine screening of blood pressure in normal children or teenagers has no prophylactic value'. With new evidence it seems likely that this view should be changed.

References

- Beresford, S. A. A., and Holland, W. W. (1973). Levels of blood pressure in children: a familial study. *Proceedings of the Royal Society of Medicine*, **66**, 1009-1011.
- Berry, C. L. (1969). Changes in the wall of the pulmonary artery after banding. *Journal of Pathology and Bacteriology*, **99**, 29-32.
- Berry, C. L., Gosling, R. G., Laogun, A. A., and Bryan, E. (1976). Anomalous iliac compliance in children with a single umbilical artery. *British Heart Journal*, **38**, 510-515.
- Berry, C. L., and Greenwald, S. E. (1976). The effects of hypertension on the static mechanical properties and chemical content of the rat aorta. *Cardiovascular Research*, **10**, 437-451.
- Berry, C. L., Looker, T., and Germain, Jocelyn (1972). Nucleic acid and scleroprotein content of the developing human aorta. *Journal of Pathology*, **108**, 265.
- Berry, C. L., Greenwald, S. E., and Rivett, J. (1975). Static mechanical properties of the developing and mature rat aorta. *Cardiovascular Research*, **9**, 669-678.
- Bevan, R. D. (1976). An autoradiographic and pathological study of cellular proliferation in rabbit arteries correlated with an increase in arterial pressure. *Blood Vessels*, **13**, 100-128.
- British Medical Journal* (1973). Detection of hypertension in childhood. **3**, 365-366.
- Brook, C. G. D. (1972). Evidence for a sensitive period in adipose-cell replication in man. *Lancet*, **2**, 624-627.
- Bryan, E. M., and Kohler, H. G. (1974). The missing umbilical artery. I. Prospective study based on a maternity unit. *Archives of Disease in Childhood*, **49**, 844-852.
- Buck, C. W. (1973). The persistence of elevated blood pressure first observed at age five. *Journal of Chronic Diseases*, **26**, 101-104.
- Burton, A. C. (1954). Relation of structure to function of tissues of the wall of blood vessels. *Physiological Reviews*, **34**, 619-642.
- Chenoweth, A. C. (1973). High blood pressure: a national concern. *Journal of School Health*, **43**, 307-308.
- de Swiet, M., Fayers, P., and Shinebourne, E. A. (1976). Blood pressure survey in a population of newborn infants. *British Medical Journal*, **2**, 9-11.
- Dible, J. H. (1964). The ageing and collateral peripheral artery. *Lancet*, **1**, 520-523.
- Dobbing, J. (1970). Undernutrition and the developing brain. The relevance of animal models to the human problem. *American Journal of Diseases of Children*, **120**, 411-415.
- Dobbing, J., and Sands, J. (1970). Timing of neuroblast multiplication in developing human brain. *Nature (London)*, **226**, 639-640.
- Dube, S. D., Kapoor, S., Ratner, H., and Tunich, F. L. (1975). Blood pressure studies in black children. *American Journal of Diseases of Children*, **129**, 1177-1180.
- Edelman, R., Suskind, R., Olson, R. E., and Sirisinha, S. (1973). Mechanisms of defective delayed cutaneous hyper-sensitivity in children with protein-calorie malnutrition. *Lancet*, **1**, 506-509.
- Epstein, M. L., Goldberg, S. J., Allen, H. D., Konecke, L., and Wood, J. (1975). Great vessel, cardiac chamber, and wall growth patterns in normal children. *Circulation*, **51**, 1124-1129.
- Finnerty, F. A., Jr. (1971). Hypertension is different in blacks. *Journal of the American Medical Association*, **216**, 1634-1635.
- Fry, J. (1974). Natural history of hypertension. A case for selective non-treatment. *Lancet*, **2**, 431-433.
- Garn, S. M., Rahmann, C. G., and Wagner, B. (1967). Continuing bone growth throughout life, a general phenomenon. *American Journal of Physical Anthropology*, **26**, 313-317.
- Gosling, R. D., and King, D. H. (1975). Ultrasonic angiography. In *Arteries and Veins*, p. 61. Ed. by A. W. Marcus and L. Adamson. Churchill Livingstone, London.
- Graham, A. W., Hines, E. A., Jr., and Gage, R. P. (1945). Blood pressures in children between the ages of five and sixteen years. *American Journal of Diseases of Children*, **69**, 203-207.
- Greenwald, S. E., de Swiet, M., and Berry, C. L. (1978). Distensibility of the aorta in newborn infants. *Ultrasound in Medicine and Biology* (in press).
- Gryfe, C. I., Exton-Smith, A. N., Payne, P. R., and Wheeler, E. F. (1971). Pattern of development of bone in childhood and adolescence. *Lancet*, **1**, 523-526.
- Hahn, L. (1952). The relationship of blood pressure to weight, height, and body surface area in schoolboys aged 11 to 15 years. *Archives of Disease in Childhood*, **27**, 43-53.
- Haworth, S. G. (1976). Structural changes in the pulmonary circulation in congenital heart disease in early infancy. M.D. Thesis, University of London.
- Jackson, G., Pierscianowski, T. A., Mahon, W., and Condon, J. (1976). Inappropriate antihypertensive therapy in the elderly. *Lancet*, **2**, 1317-1318.
- Journal of the American Medical Association* (1967). Effects of treatment on morbidity in hypertension. I. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. Veterans Administration Co-operative Study Group on Antihypertensive Agents. **202**, 1028-1034.
- Journal of the American Medical Association* (1970). Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. Veterans Administration Co-operative Study Group on Antihypertensive Agents. **213**, 1143-1152.
- Journal of the Royal College of Physicians of London* (1976). Prevention of Coronary Artery Disease. Report of a Joint Working Party of the Royal College of Physicians of London and the British Cardiac Society. **10**, 213-275.
- Londe, S. (1966). Blood pressure in children as determined under office conditions. *Clinical Pediatrics*, **5**, 71-78.
- Londe, S. (1968). Blood pressure standards for normal children as determined under office conditions. *Clinical Pediatrics*, **7**, 400-403.
- Londe, S., Bourgoigne, J. J., Robson, A. M., and Goldring, D. (1971). Hypertension in apparently normal children. *Journal of Pediatrics*, **78**, 569-577.
- Meade, T. W., and Chakrabarti, R. (1972). Arterial disease research: observations or intervention. *Lancet*, **2**, 913-916.
- Meyer, W. W., and Lind, J. (1974). Iliac arteries in children with a single umbilical artery. Structure, calcifications and early atherosclerotic lesions. *Archives of Disease in Childhood*, **49**, 671-679.
- Morris, J. N. (1973). Four cheers for prevention. *Proceedings of the Royal Society of Medicine*, **66**, 225-232.
- Newton-John, H. F., and Morgan, D. B. (1968). Osteoporosis: disease or senescence? *Lancet*, **1**, 232-233.

- Reid, D. D., Hamilton, P. J. S., McCartney, P., Rose, G., Jarrett, R. J., and Keen, H. (1976). Smoking and other risk factors for coronary heart disease in British civil servants. *Lancet*, **2**, 979-984.
- Rose, G. (1962). A study of blood pressure among Negro children. *Journal of Chronic Diseases*, **15**, 373-380.
- Ross, R. (1971). The smooth muscle cell. II. Growth of smooth muscle in culture and formation of elastic fibers. *Journal of Cell Biology*, **50**, 172-186.
- Ross, R., and Glomset, J. A. (1973). Atherosclerosis and the arterial smooth muscle cell. *Science*, **180**, 1332-1339.
- Ross, R., and Klebanoff, S. J. (1971). The smooth muscle cell. I. In vivo synthesis of connective tissue proteins. *Journal of Cell Biology*, **50**, 159-171.
- Sackett, D. L. (1974). Screening for disease: cardiovascular disease. *Lancet*, **2**, 1189-1191.
- Salans, L. B., Cushman, S. W., and Weismann, R. E. (1973). Studies of human adipose tissue. Adipose cell size and number in nonobese and obese patients. *Journal of Clinical Investigation*, **52**, 929-941.
- Smythe, P. M., Schonland, M., Brereton-Stiles, G. G., Coovadia, H. M., Grace, H. J., Loening, W. E. K., Mafoyané, A., Parent, M. A., and Vos, G. H. (1971). Thymolymphatic deficiency and depression of cell-mediated immunity in protein-calorie malnutrition. *Lancet*, **2**, 939-944.
- Stark, J., Berry, C. L., and Silove, E. D. (1972). The evaluation of materials used for pulmonary artery banding. *Annals of Thoracic Surgery*, **13**, 163-169.
- Taylor, M. G. (1964). Wave travel in arteries and the design of the cardiovascular system. In *Pulsatile Blood Flow*, pp. 343-372. Ed. by E. O. Attinger. McGraw Hill, New York, Toronto, and London.
- Voors, A. W., Foster, T. A., Frerichs, R. R., Webber, L. S., and Berenson, G. S. (1976). Studies of blood pressures in children, ages 5-14 years, in a total biracial community. *Circulation*, **54**, 319-327.
- Weiss, L. (1974). Aspects of the relation between functional and structural cardiovascular factors in primary hypertension. *Acta Physiologica Scandinavica*, Suppl. **409**.
- Whyte, H. M. (1975). Potential effect on coronary heart disease morbidity of lowering the blood cholesterol. *Lancet*, **1**, 906-910.
- Wright, I. (1963). The microscopical appearance of human peripheral arteries during growth and ageing. *Journal of Clinical Pathology*, **16**, 499-522.
- Zinner, S. H., Levy, P. S., and Kass, E. H. (1971). Familial aggregation of blood pressure in childhood. *New England Journal of Medicine*, **284**, 401-404.

Requests for reprints to Professor C. L. Berry, Department of Morbid Anatomy, The London Hospital, London E1 1BB.