Hypertensive disorders of pregnancy affect up to 15% of pregnancies and the most severe form, pre-eclampsia, is the leading cause of maternal death in the UK today. Pre-eclampsia is a multisystem disorder affecting virtually every organ and system in the body, with hypertension and proteinuria, the traditional diagnostic features, representing two facets of a complex pathophysiological process. The common pathological feature of the disease, whether in the decidual vessels of the placental bed, renal microvasculature, liver, heart or cerebral circulation, is vascular endothelial damage and dysfunction. Before new ways of preventing or ameliorating hypertensive disorders of pregnancy can be found, we must first understand the pathophysiological mechanisms underlying the clinical problem. This review summarizes the evidence that endothelial dysfunction plays a key role in hypertensive disorders of pregnancy and will focus on the most severe form, pre-eclampsia.

Three types of hypertension can occur in pregnancy. First, pregnancy may occur in patients with pre-existing hypertensive disease. Second and rarely, hypertension may result from a coincidental development of a new medical cause occurring in pregnancy, such as phaeochromocytoma. Third, there are women who are normotensive before pregnancy and in early pregnancy but who develop hypertension during pregnancy that remits within a few months of delivery; these women have pregnancy-induced hypertension. Pre-eclampsia is a severe form of pregnancy-induced hypertension and occurs at frequencies of between 1% and 5%. It is characterized by high blood pressure in late pregnancy (90 mmHg or a rise of 25 mmHg) and proteinuria (0.3 g per 24 h) with a wide range of pathophysiological organ and system disturbances. It can lead to the occurrence of epileptic-like grand mal convulsions (eclampsia) in about 0.1% of pregnancies. Cerebral vascular accident is the most common cause of death. The disease has no known cause and can only be cured by delivery of the fetus and placenta. Pre-eclampsia remains the major cause of maternal death in the UK to-day; it is also a major contributor to maternal and perinatal morbidity and perinatal mortality. Furthermore, recent epidemiological evidence suggests that intrauterine growth retardation (IUGR), the risk of which is increased in pre-eclampsia, may be linked to the development of cardiovascular disease in adult life. Despite increasing knowledge of its pathophysiological processes, the aetiology of this condition remains obscure. The common pathological feature of the disease, whether in the placental bed, renal microvasculature or cerebral circulation, is vascular endothelial damage and dysfunction.

General reviews on the pathophysiology and aetiology of pregnancy-induced hypertension have been published elsewhere (Greer, 1992; Lyall and Greer, 1994, 1995a).

**The endothelium**

The vascular endothelium plays an active role in the control of haemostasis and thrombosis (Table 1). It produces prostacyclin and nitric oxide (NO) which can inhibit the activation of platelets and neutrophils and substances, such as tissue plasminogen activator (tPA), that prevent or limit coagulation and vascular damage. The glycosaminoglycans of the endothelial cell plasma membrane are rich in heparin sulfate and so bind antithrombin, increasing its affinity for thrombin. This allows rapid clearing of thrombin. The endothelium also controls coagulation by surface expression of thrombomodulin which binds to thrombin, simultaneously lowering its affinity for fibrinogen and increasing its ability to activate protein C. Protein C is an anticoagulant that inactivates factor Va, factor VIII and plasminogen activator inhibitor. Endothelial cells also contribute to the action of protein C by secreting its co-factor, protein S. Endothelial cells are a source of adenine nucleotides, which under certain circumstances cause vasodilatation.

Conversely, the endothelium can render itself thrombogenic by secreting von Willebrand's factor, which stabilizes factor VIII and acts as a cofactor for the adhesion of platelets. It also secretes platelet-activating factor, an important mediator of platelet/fibrin formation. These latter factors would normally promote local coagulation and repair at the site of injury. The endothelium can contribute directly to thrombosis by the release of plasminogen activator inhibitor-1 (PAI-1), which counteracts the fibrinolytic effects of tissue type plasminogen activator (t-PA), preventing or limiting coagulation and vascular damage, and thus promoting blood coagulation (Fig. 1). These events have been reviewed in detail by Bloom et al. (1994).

The endothelium also influences vascular tone by releasing vasodilator substances such as prostacyclin and NO, and vasoconstrictors such as endothelin. It is also intimately linked to the actions of the vasodilator atrial natriuretic peptide (ANP) and to the renin–angiotensin system. Endothelial cells also express ectopeptidases that can convert angiotensin I to angiotensin II, inactivate bradykinin and produce active endothelin from big endothelin. Normally, the endothelium, platelets and neutrophils will interact homeostatically. It is well known that denudation of the endothelium will result in thrombosis;
endothelial dysfunction may have similar effects and could transform the endothelium from a nonthrombogenic to a thrombogenic surface. The endothelium can also regulate neutrophil and platelet adhesion and activation through the expression and secretion of cell adhesion molecules. Furthermore, cytokines acting on or released by endothelial cells can affect many aspects of endothelial function. Endothelial cells can also modify low density lipoproteins (LDL), giving rise to damaging oxidized LDL, and damaged endothelial cells are also a source of growth factors.

Nitric oxide

Nitric oxide (NO) plays an important role in the control of systemic blood pressure (Knowles and Moncada, 1994). The endothelial nitric oxide synthase (eNOS) generates NO continually, which diffuses to the underlying smooth muscle, increasing cGMP production and thus mediating vasodilatation (Fig. 2). Nitric oxide is also an inhibitor of platelet and neutrophil activation and impairment of its formation in the vessel wall will not only lead to neutrophil activation and vasoconstriction in the maternal circulation but will also favour platelet adhesion, aggregation and the consequent release of vasoconstrictor substances.

During pregnancy a number of changes occur in the cardiovascular system. Blood pressure declines in the first trimester, reaches a nadir in midpregnancy and then slowly increases to values comparable with those in the nonpregnant state. Cardiac output increases by 40% and this is maintained throughout the pregnancy. The fall in blood pressure reflects a reduction in systemic vascular resistance. In the second half of pregnancy, the increase in blood pressure results from an increase in systemic vascular resistance. Normal pregnancy is also characterized by decreased reactivity to pressor stimuli.

What is the evidence that nitric oxide is involved in the circulatory changes of normal and indeed abnormal pregnancy? The synthesis of NO and cGMP increases from prepregnant amounts during gestation in rats (Conrad et al., 1993). Plasma concentrations and urinary excretion of cGMP are also increased during human pregnancy (Kopp et al., 1977). Excess production of NO may also explain the blunted pressor response to noradrenaline seen during normal pregnancy. Although information on the role of NO in human pregnancy is limited, it is known that NO contributes to vascular tone in the human placental villus vascular tree (Myatt et al., 1991). The human feto-placental circulation is not innervated and vasoactive factors such as NO are likely to be important in maintaining feto-placental blood flow. An endothelial isoform of NOS has been characterized in the human placenta and immunolocalized to the endothelium of umbilical, chorionic plate and stem villous vessels but not to terminal villous vessels in which there is no underlying smooth muscle (Myatt et al., 1993). Immunostaining is also found in syncytiotrophoblast, but not in the underlying progenitor cytotrophoblast cells. Since it is the syncytiotrophoblast that lines the placental surface and is in direct contact with maternal blood, NO produced by the syncytiotrophoblast may prevent platelet and leucocyte adhesion within the intervillous space.

In established pre-eclampsia, cardiac output is reduced and plasma volume is contracted, while systemic vascular resistance is noticeably raised. This raised systemic vascular resistance is not sympathetically mediated. The response to vasopressor

| Table 1. Endothelial cell products and their main roles in regulating vascular homeostasis |
|---------------------------------|--------------|----------------|
| Endothelial cell product       | Secreted     | Surface expressed/bound |
| Prostacyclin                   | +            | Platelet and neutrophil inhibition |
| Nitric oxide                   | +            | Platelet and neutrophil inhibition |
| Endothelin                     | +            | Vasodilator |
| Ectonucleotidases              | +            | Vascular tone, platelet function |
| Platelet-activating factor     | +            | Platelet activation |
| von Willebrand factor          | +            | Leucocyte function |
| Tissue factor                  | +            | Promotes coagulation, platelet adhesion |
| Binding sites for coagulation  | +            | Promotes coagulation |
| factors Va, Xa, IXa             | +            | Promotes coagulation |
| Thrombomodulin                 | +            | Promotes leucocyte adhesion |
| Glycosaminoglycans             | +            | Inhibits coagulation |
| Protein C, protein S           | +            | Inhibits coagulation |
| Tissue plasminogen activator   | +            | Increases fibrinolysis |
| Plasminogen activator inhibitor| +            | Inhibits fibrinolysis |
| Cell adhesion molecules:       | +            | Numerous effects on immune system |
| VCAM-1, P-Selectin,            |              | |
| ICAM-2, E-Selectin, PECAM-1    |              | |
| Cytokines, eg interleukin (IL)-1, IL-6, IL-8, colony-stimulating factors | + | |

VCAM: vascular endothelial cell adhesion molecule; ICAM: intercellular adhesion molecule; PECAM: platelet endothelial cell adhesion molecule.
agents is also exaggerated. It has been hypothesized that an imbalance in NO production may be related to these abnormalities. Studies in animals seem to support this hypothesis. In pregnant rats, chronic blockade of NO synthesis increases blood pressure, induces proteinuria and IUGR, and reduces expansion of maternal plasma volume space (Molnar et al., 1994).

In humans, however, the evidence is conflicting. The ability of perfused umbilical vessels to release NO in response to bradykinin is reduced in pregnancy-induced hypertension (Pinto et al., 1991). However, studies on relaxation responses in maternal resistance arteries suggest that the NO-mediated component of endothelium-dependent relaxation is unaffected in pre-eclampsia (McCarthy et al., 1993). Synthesis of NO can be determined indirectly by measuring concentrations of nitrites and nitrates, oxidation products of NO. Cameron et al. (1993) showed that concentrations of urinary nitrites and nitrates in
normal pregnant and hypertensive pregnant women were similar; however, in hypertensive women there was a direct correlation between urinary nitrite/nitrate excretion and the change in systolic blood pressure, which suggests that a compensatory increase in NO synthesis occurs in pregnant women to maintain homeostasis. In agreement with this, serum concentrations of nitrites are unaltered in the maternal circulation in pre-eclampsia (Lyall et al., 1995a). However, other studies have reported reduced circulating concentrations of nitrites in women with pre-eclampsia (Seligman et al., 1994). It may be that these discrepancies reflect the limitations of this assay, which is affected by factors such as diet, or that larger studies are required to obtain more reliable data. Studies in vitro have shown that endothelial cell nitrite production is higher after exposure to plasma from patients with pre-eclampsia compared with plasma from normal pregnant women (Baker et al., 1995). Nitric oxide synthesis can be inhibited by arginine analogues, including N\textsuperscript{\text{\textnd}}N\textsuperscript{\text{\textnd}}-dimethylarginine (ADMA), which is present both in human plasma and urine and can be released from endothelial cells in vitro. Concentrations of ADMA are increased in patients with pre-eclampsia (Fickling et al., 1993). Increased vascular resistance in the fetoplacental circulation is also a characteristic of pre-eclampsia and IUGR pregnancies. Infusion of the NO donor, glycerol trinitrate (GTN) has been shown to improve uterine artery blood flow in pregnancy, whereas other vasodilators have only minor effects (Ramsay et al., 1994). Whether improving uterine artery blood flow will also improve maternal or fetal outcome remains to be established. Results of studies on the fetoplacental unit are also conflicting. Increased immunostaining for eNOS in stem villous vessels and the appearance of eNOS staining in the endothelium of small vessels of the villous tree occurs in pre-eclampsia (Myatt et al., 1995). In agreement with this, concentrations of nitrites in umbilical vein are also increased (Lyall et al., 1995a), supporting the hypothesis that increased NO synthesis may be an adaptive response to increased blood flow in the uteroplacental circulation. In contrast, Wang et al. (1994) found no differences in the production of NO from placental tissues from women with pre-eclampsia, and Kovacs et al. (1994) reported that umbilical venous plasma concentrations of cGMP were reduced in women with pre-eclampsia and pregnancy-induced hypertension. The only study to investigate enzyme activity showed that placental villous homogenates from pregnancies complicated by pre-eclampsia and fetal growth retardation had lower activities of NOS than did normal pregnancies (Morris et al., 1995). In summary, generation of NO is increased in normal pregnancy (for a review of the role of NO in the uterus during pregnancy see Norman and Cameron, 1996); however, convincing evidence that NO plays a role in the endothelial dysfunction of pre-eclampsia and other hypertensive disorders of pregnancy remains contentious.

**Prostanoids**

Prostacyclin (PGI\textsubscript{2}), a mainly endothelial-derived prostanoid, synthesized from arachidonic acid (Fig. 3) is a potent vasodilator, an inhibitor of platelet aggregation and a stimulator of renin secretion. In contrast, thromboxane A\textsubscript{2} (TXA\textsubscript{2}), which is released by platelets and metabolized from endoperoxides by thromboxane synthase, is a potent vasoconstrictor and platelet aggregating agent. Thus PGI\textsubscript{2} and TXA\textsubscript{2} have opposing effects on thrombosis and haemostasis.

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**Fig. 2.** Schematic diagram showing constitutive release of nitric oxide (NO) in endothelial cells. In endothelial cells, shear stress and agonists such as acetylcholine, adenosine diphosphate, thrombin, bradykinin and 5-hydroxytryptamine increase intracellular calcium and activate NO synthase (eNOS) to form NO from L-arginine. The by-product from the reaction is L-citrulline. In blood, NO is readily oxidized by the superoxide anion or bound to haemoglobin and to SH groups on albumin and thiols. NO readily diffuses from the endothelium into the underlying vascular smooth muscle where it increases cGMP concentrations thus mediating vasorelaxation. NO also inhibits neutrophil and platelet activation at the endothelial surface.
The pathological features of pre-eclampsia include vasoconstriction, platelet consumption, and low renin secretion. Women with pre-eclampsia are very sensitive to exogenous angiotensin II infusions when compared with normal pregnant women. The insensitivity to angiotensin II seen in normal pregnancy can be abolished by treatment with a cyclooxygenase inhibitor, and enhanced by infusion of prostacyclin or prostaglandin E₂ (Broughton-Pipkin et al., 1984). This suggests that in normal pregnancy, angiotensin II may be balanced by the action of vasodepressor prostaglandins such as prostacyclin. A deficiency of prostacyclin may therefore result in the angiotensin II sensitivity seen in pre-eclampsia. Maternal vascular prostacyclin production is reduced in pre-eclampsia (Bussolino et al., 1980). However, TXB₂ production (TXB₂ is the metabolite of TXA₂) is increased (Wallenburg and Rotmans, 1982). The resulting imbalance between the prostanoids, prostacyclin and thromboxane is likely to contribute to the enhanced platelet reactivity and vascular damage seen in pre-eclampsia.

On the fetal side, production of prostacyclin from cord vessels is reduced in pre-eclampsia (Walsh, 1985). Furthermore, placentae from these pregnancies have been shown to produce more thromboxane A₂ and less prostacyclin than those from normal pregnancies (Walsh, 1985). Umbilical arteries from pregnancies complicated by pre-eclampsia are unresponsive to a stimulus of prostacyclin production when compared with normal umbilical arteries (McLaren et al., 1987). Since the umbilical artery is not innervated, it may depend on humoral control of blood flow by prostanooids to maintain the low pressure–high flow fetoplacental circulation. Failure to produce prostacyclin in response to physiological stimulation may result in increased umbilical artery resistance due to vasoconstriction, especially in the face of increased thromboxane production by the placenta. The deficiency of prostacyclin and the resulting prostanooid imbalance may also allow vascular damage to occur unchecked. The interactions between PG₁ and TX₂ have provided the rationale for low dose aspirin therapy as a treatment for pre-eclampsia. However, the biggest trials to date suggest that aspirin has limited benefit in treating or preventing pre-eclampsia (reviewed in Lyall and Greer, 1994).

Platelets
Platelets play a crucial role in the pathophysiology of pre-eclampsia by promoting vascular damage and obstruction, leading to tissue ischaemia and further damage (Greer, 1992). There is considerable evidence implicating platelets in the pathophysiology of pre-eclampsia. The circulating platelet count is reduced (Redman et al., 1978), reflecting a reduced platelet lifespan. The reduction in platelet count appears to be due to increased platelet consumption associated with low grade disseminated intravascular coagulation. The platelet specific protein β-thromboglobulin, a marker of platelet activation in vivo, is also increased (Socol et al., 1985). This correlates with proteinuria and serum creatinine (Socol et al., 1985), and suggests a link between platelet activation and renal microvascular damage. Increased platelet thromboxane A₂ production also occurs in pre-eclampsia (Wallenburg and Rotmans, 1982). Delacretaz et al. (1995) reported reduced NOS activity in platelets from women with pre-eclampsia and suggested that this leads to enhanced vasoconstriction.

Neutrophil activation
Neutrophils contribute to vascular damage in nonpregnant individuals. Activated neutrophils release substances that can mediate vascular damage, including the contents of neutrophil granules such as elastase and other proteases. Toxic oxygen species are released, and can produce membrane lipid peroxidation, lysis of endothelial cells, and increased vascular permeability and reactivity. However, before neutrophils and other leucocytes can mediate vascular damage, they must first undergo a series of cellular events to adhere to the endothelial surface (Harlan and Liu, 1992). They roll along the endothelial surface of the vessel wall and, at specific sites, become securely flattened before passing into the subendothelial space (Fig. 4a). Adherence of neutrophils to the endothelium is mediated by cell adhesion molecules expressed on the endothelium and the circulating leucocytes. The majority of cell adhesion molecules identified fall into one of four families: the immunoglobulin superfamily, the selectins and the cadherins; the former three being important in leucocyte–endothelial interactions (Fig. 4b). On the endothelial surface, the major cell adhesion molecules involved in leucocyte recruitment to the
endothelium include E-selectin and P-selectin, intercellular adhesion molecule 1 and 2 (ICAM-1 and ICAM-2) and vascular endothelial cell adhesion molecule 1 (VCAM-1). E-selectin, VCAM-1 and ICAM-1 are either not or only minimally expressed on endothelial cells, but expression can be upregulated by certain pro-inflammatory cytokines, such as tumour necrosis factor α (TNF-α) and interleukin (IL-1) (see Haskard, 1994 for a detailed review). Cell adhesion molecules can also be shed from the endothelial surface and so exist as circulating forms. Circulating concentrations of adhesion molecules appear to reflect their endothelial expression. Increased tissue expression and increased circulating concentrations of endothelial adhesion molecules are also associated with diseases involving endothelial damage and leucocyte activation.

Neutrophils are activated in pre-eclampsia. Concentrations of neutrophil elastase, a marker of neutrophil activation in vivo, are raised in pre-eclampsia, but this increase is confined to the maternal circulation. This correlates with the increase in plasma von Willebrand factor and is associated with an increase in endothelial endothelin concentrations (Greer et al., 1991). Neutrophil activation may therefore contribute directly to the vascular lesions noted in pre-eclampsia, for example in the placental bed. Elastase positive neutrophils can be found in significantly increased numbers in the decidua of the placental bed in women with pre-eclampsia, and this correlates with the increase in plasma urate, an established marker of disease activity (Butterworth et al., 1991). In addition to directly bringing about endothelial damage, neutrophils will interact with platelet, coagulation and complement systems. Since increased expression of cell adhesion molecules is associated with diseases involving leucocyte activation, the possibility arises that cell adhesion molecules may be involved in the neutrophil activation that occurs in pre-eclampsia. In support of this, circulating concentrations of the cell adhesion molecules E-selectin and VCAM-1 are higher in the circulation of women with pre-eclampsia compared with that of non-pregnant women (Lyall et al., 1994; Lyall and Greer, 1995b). Furthermore, this effect appears to be confined to the maternal circulation, since surface expression of these cell adhesion molecules is similar in placentae obtained from pregnancies complicated by pre-eclampsia and from normal pregnancies (Lyall et al., 1995b). Although the mechanisms of neutrophil activation

**Fig. 4.** (a) Simplified representation of how cell adhesion molecules mediate neutrophil adhesion to the endothelium. (b) Schematic representation of the three major classes of cell adhesion molecules involved in leucocyte–endothelial interactions. Selectins are characterized by an N-terminal lectin region, an epidermal growth factor-like domain (EGF), a number of units homologous to complement binding proteins (CRD) and a transmembrane domain and a short cytoplasmic tail (CD). Selectins have been named after the cell type in which each molecule was first described: L-selectin (leucocyte), E-selectin (endothelial) and P-selectin (platelets). The lectin domain interacts with carbohydrate structures on the cells that it binds to. Selectins are involved in leucocyte rolling. Integrins are a large family of noncovalently linked heterodimeric glycoproteins, some of which are ligands for immunoglobulins. Each heterodimer is composed of a noncovalently linked α chain and β chain. The β chain contains a large loop stabilized by disulfide bonds and α chains contain divalent cation binding sites. Integrins are thought to immobilize leucocytes that are rolling, leading to spreading on the endothelial surface. The immunoglobulin family include a number of cell membrane glycoproteins with structural homology to antibodies. This family, which includes platelet endothelial cell adhesion molecule 1 (PECAM-1), vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1, 2 and 3 (ICAM-1, -2 and -3), shares the immunoglobulin domain composed of 970–1100 amino acids arranged in a sandwich of two sheets of anti-parallel β strands stabilized by a central disulfide bond.
are not known, pro-inflammatory cytokines can activate neutrophils and increase expression of cell adhesion molecules on endothelial cells. Circulating concentrations of the cytokine IL-6 are increased in plasma of women with pre-eclampsia (Greer et al., 1994; Vince et al., 1995). Concentrations of TNF-α and its soluble receptors are also increased in pre-eclampsia, although increases in TNF-α may be linked to an extreme form of this disease associated with very low platelet counts (HELLP syndrome) (Greer et al., 1994; Vince et al. 1995). Increased concentrations of IL-1 receptor antagonist, a naturally occurring inhibitor of IL-1, also occur in pre-eclampsia, suggesting a protective mechanism to counteract the effects of IL-1 (Greer et al., 1994).

Pre-eclampsia is also associated with a factor that enhances superoxide production from neutrophils (Tsukimori et al., 1987). High concentrations of reactive oxygen species can inhibit cyclo-oxygenase and prostacyclin synthase, thus inhibiting prostacyclin production. High concentrations of reactive oxygen species can reorientate the arachidonic acid pathway in the cell away from the production of prostacyclin towards thromboxane A₂. Furthermore, plasma concentrations of anti-oxidants, which may reflect increased activity of reactive oxygen species, are also reduced in women with pregnancy-induced hypertension and these positively correlate with prostanoids, supporting a role for reactive oxygen species in abnormal PGH₂/TXB₂ production (Chen et al., 1993). Thus, neutrophil activation may account for the necrotizing arteriopathy of pre-eclampsia and may also explain several other features of the disease, such as prostacyclin deficiency and enhanced thromboxane production.

Lipids, vascular endothelial damage and pre-eclampsia

There is much evidence linking hyperlipidaemia to endothelial dysfunction in nonpregnant women (Stewart and Monge, 1993). Normal pregnant women have hyperlipidaemia and some studies suggest that this may be enhanced in pre-eclampsia (Maseki et al., 1981), suggesting that abnormal lipid metabolism may have a role in this disorder. Furthermore, lipid peroxide products are increased in serum of women with pre-eclampsia (Maseki et al., 1981) and can inhibit prostacyclin synthase but not thromboxane synthase. Women with pre-eclampsia also have a higher mean titre of autoantibodies to oxidized low-density lipoproteins (Branch et al., 1994).

One of the key events in the pathogenesis of atherosclerotic lesions is the focal accumulation of lipid- (in particular the oxidized form of low density lipoprotein) laden foam cells (macrophages) beneath an intact endothelial lining. In pre-eclampsia, decidual vessels show fibrinoid necrosis of the vessel wall and focal accumulation of lipid-laden macrophages, similar to the situation in atherosclerosis, suggesting that enhanced lipid peroxidation may be involved in the foam cell formation.

Endothelins

The endothelins are the most potent vasoconstrictors known, exerting their vasoconstricting effects via ET₁ receptors on smooth muscle cells. By acting on ET₂ receptors, endothelins can release NO and prostacyclin from the endothelium, allowing inhibition of platelet activation. Endothelins can cause release of tissue plasminogen activator leading to increased fibrinolytic activity. There are many reports describing increased circulating concentrations of endothelin in women with pre-eclampsia (Taylor et al., 1990), and these changes correlate with von Willebrand factor and fibrinectin concentrations (Greer et al., 1991). These data are in keeping with the extent of the endothelium damage and dysfunction that occurs in this disorder.

Coagulation changes and endothelial dysfunction

Blood coagulation consists of a complex series of events that give rise to insoluble fibrin. The fibrinolytic enzyme system is the physiological mechanism that removes this fibrin (Fig. 1). Clearly an imbalance between these two processes may lead to inappropriate thrombosis. Activation of the coagulation cascade is usually associated with activation of the fibrinolytic system, and this is true for pre-eclampsia (Davies and Prentice, 1992). Widespread deposition of fibrin associated with vascular damage, such as acute atherosis in the placental bed or glomerular endotheliosis, has long been known to be a pathological feature of pre-eclampsia and suggests that the coagulation system is activated (Davies and Prentice, 1992; Greer, 1992). This probably represents a secondary phenomenon consequent upon vascular damage. Routine coagulation tests are essentially normal, unless pre-eclampsia is complicated by full blown disseminated intravascular coagulation (Davies and Prentice, 1992). Increased concentrations of fibrinopeptide A suggest that fibrinogen breakdown occurs in severe disease. Fibrinogen itself also increases in hypertensive compared with normal pregnancy, although this may simply be an acute phase reactant increasing in response to the disease in general. There is an increase in Factor VIIIc activity, but the increase in von Willebrand factor antigen is greater. Factor VIII is produced by the liver, while von Willebrand factor is synthesized by the vascular endothelium and increases after endothelial damage.

The most precise assays of plasminogen activators and their inhibitors have shown unchanged plasma plasminogen activator, but increased concentrations of tissue plasminogen activator in plasma of women with pre-eclampsia (Estelles et al., 1987). This may be due to stimulation of or damage to the endothelium. This increase in tissue plasminogen activator is accompanied by an increase in plasminogen activator inhibitors 1 and 2 (Estelles et al., 1987). Plasminogen activator inhibitor 2 is produced only from the placenta and may again reflect placental vascular damage and predispose to local thrombosis by local inhibition of fibrinolysis in the abnormal vessels of the placental bed. It should be noted that all studies have not been consistent.

The increase in fibrinopeptide Bβ₁₋₄₂ provides additional evidence of fibrinolytic activation. Plasminogen and the inhibitor of plasmin, α₂-antiplasmin, have also been found to be reduced (Davies and Prentice, 1992) in keeping with fibrinolytic activation. This increase in fibrinolysis may be a response to intravascular coagulation, which may be prevented from reaching its full potential by the concomitant increase in intravascular inhibitors of plasminogen activation.

There are no major changes in most of the individual coagulation factors (reviewed in Greer, 1992), suggesting that, in
general, only minimal coagulation activation occurs, although this may progress to complete disseminated intravascular coagulation in severe cases.

The origins of endothelial dysfunction
The aetiology of pre-eclampsia is likely to be found in early pregnancy. In pre-eclampsia, the normal process of trophoblast invasion of maternal spiral arteries is impaired (Pijnenborg et al., 1991). Furthermore, this impaired trophoblast invasion appears to be linked to a failure of the invading trophoblast cells to express a class of integrin cell adhesion molecules (Zhou et al., 1993). Several lines of evidence suggest that impaired trophoblast invasion and hence reduced placental perfusion may lead to release of a factor(s) that brings about widespread endothelial cell activation, leading to the multisystem dysfunction that characterizes pre-eclampsia (Fig. 5). The nature of this factor is unclear but, since it diminishes after delivery (Roberts et al., 1991), it may be released from the placenta or could equally well be related to neutrophil activation. Incubation of endothelial cells in vitro with sera from pre-eclamptic women also significantly increases cellular fibronectin, an important mediator of platelet adhesion and aggregation (Taylor et al., 1991).

Diabetic pregnancy
Type 1 (insulin-dependent) diabetes mellitus (IDDM) is a chronic autoimmune disease characterized by destruction of the pancreatic β-cells. Although IDDM complicates fewer than 0.5% of all pregnancies, pregnancy in women with diabetes is associated with increased maternal morbidity due to factors such as increased caesarean section rate, polyhydramnios and pre-eclampsia. The mother may also be at risk of a deterioration in microvascular complications; however, it appears that background and possibly proliferative retinopathy improves after delivery. Similarly, although diabetic nephropathy may worsen in pregnancy, it tends to return to the pre-pregnant state after delivery. These findings suggest that there is a pregnancy-associated factor(s) that triggers deterioration of such microvascular complications.

Platelet and neutrophil activation (Greer et al., 1989) also occur in diabetic pregnancy. Neutrophil activation is present in

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**Fig. 5.** Schematic representation of trophoblast invasion of spiral arteries. Broken lines indicate trophoblast invading the vessels. It has been suggested that impaired invasion of spiral arteries in pregnancies complicated by pre-eclampsia results in release of a factor(s) into the maternal circulation, causing widespread endothelial damage and dysfunction.
nonpregnant diabetic women (Greer et al. 1989). There is also evidence of endothelial damage, as assessed by measurement of von Willebrand factor in diabetic nephropathy (Stehouwer et al., 1991). It may be that the pathophysiological process that mediates vascular damage in pre-eclampsia may also play a role in endothelial damage in diabetic pregnancy.

Conclusions

Endothelial damage and dysfunction are common features of all of the pathological features of pre-eclampsia, stimulating the activation of platelets, neutrophils and the coagulation system, and promoting further vascular damage. Activation of platelets and the coagulation system can cause endothelial damage directly, and also indirectly by activation of neutrophils. Thus, endothelial damage, the platelets and coagulation system, and neutrophils all interact. Once one of these systems is triggered, a positive feedback loop will promote vascular damage. The trigger that initiates this vicious circle is unclear. It appears to originate in the placenta or uteroplacental bed and is probably linked to the failure of trophoblast invasion, which is characteristic of the disease. This process leads to tissue ischaemia, which, in turn, activates the vicious circle described above to produce widespread endothelial damage and dysfunction. Management of pre-eclampsia at present focuses on controlling blood pressure but effective diagnosis and treatment will come only as a result of a clearer understanding of the pathogenesis of the disease.

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Vascular endothelium in pregnancy and pre-eclampsia

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