STUDIES ON LIMB BLOOD FLOW IN NORMAL AND ABNORMAL PREGNANCY

THESIS SUBMITTED FOR M.D.

I, Sheila L.B. Duncan, hereby declare that the accompanying thesis has been compiled by myself. The experimental studies to obtain the results presented were conducted personally. Initially, some of the work was carried out in collaboration with Dr. Jean Ginsburg and some of the results presented have been submitted for publication jointly :-

Peripheral Circulation in Normal Pregnancy, Cardiovascular Research (1967) In Pre

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The method of recording plethysmographic changes electrically was devised and tested in conjunction with A.G.Bernard. The apparatus described was demonstrated at the Physiological Society in December 196 and was subsequently published :- J. Physiol. (1965), 177, 39P.

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STUDIES ON LDH BLOOD FLOW IN NORMAL AND ABNORMAL PREGNANCY

by

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INTRODUCTION

Changes in cardio-vascular function are an integral feature of many obstetric disorders. Pre-eclamptic toxaemia, haemorrhage (including placental abruption) and pulmonary embolism are, at present, among the most important of the underlying causes of maternal mortality (Walker, Confidential Enquiries into Maternal Deaths in England and Wales, 1966). The prominence of pulmonary embolism as the commonest single cause of maternal death reflects not only the difficulty of diagnosis and the intractibility of treatment, but also the frequency of occurrence of venous thrombosis, which often goes unrecognised. Pregnancy associated with heart disease, both of rheumatic and congenital origin, is also an important cause of maternal mortality and morbidity. In addition, some of these disorders, notably pre-eclamptic toxaemia and placental abruption, are important causes of foetal loss (Butler and Bonham, Perinatal Mortality Report, 1963).

While these different conditions have diverse causes, they all involve the vascular system and its response to pregnancy. Hence, knowledge of the normal cardio-vascular adjustments to pregnancy is essential in understanding the aetiology of these disorders and in instituting rational therapy. However, despite many studies of generalised changes in the cardio-vascular system in pregnancy in terms of cardiac output, blood volume and blood pressure (discussed in a subsequent section of this thesis), little is known of the mechanisms initiating or maintaining these changes. Indeed, the factors which

maintain blood pressure close to non-pregnant levels despite major anatomical alterations in the vascular bed and changes in cardiac output are not fully understood.

Similarly, when hypertension occurs in pregnancy, additional adjustments of vascular function must occur to maintain the blood pressure at the higher levels, but the nature and distribution of these superimposed changes have not yet been explained.

Relatively little is known of the regional distribution of cardio-vascular changes at different stages of pregnancy and in some of the regions studied the findings have been conflicting. In particular, studies concerning limb blood flow in pregnancy are few and the results conflicting. This relative paucity of information about changes in limb circulation in pregnancy is surprising since:-

1) skin and muscle blood flow account for approximately 30% of the cardiac output (Wade and Bishop, 1962) and changes in these vascular beds in pregnancy would materially affect the remainder of the circulatory system.
2) Any generalised alteration in vascular tone in normal or in abnormal pregnancy would be detectable in the peripheral circulation.
3) The limbs are readily accessible and determination of limb blood flow can be carried out with relative ease.

In recent years, the vital role of the venous system in controlling venous return and hence cardiac output by active rather than passive participation has been increasingly recognised (Alexander 1954,

Sharpey-Schafer 1961, Folkow and Mellander 1964). Assumptions concerning changes in the venous system in pregnancy appear frequently in the literature (Tenney and Little 1961, Browne and McClure Browne 1963, Johnstone and Kellar 1965), but are supported by little reliable data.

It was evident, therefore, that investigation into the peripheral circulation in pregnancy was justified. A study has been made into:-

1) Resting limb blood flow in different segments in normal women during pregnancy and the puerperium and in women with non-hypertensive medical disorders.
2) A parallel study in women with hypertension in pregnancy.
3) Reaction of the forearm resistance vessels to temporary ischaemia combined with mild exercise in both healthy women and those with hypertension in pregnancy.
4) Venous tone of the forearm vessels in healthy women and in those with heart disease in pregnancy and the puerperium.

HISTORICAL ASPECTS

Until about a century ago, the mechanical problems of parturition and the dread of puerperal sepsis so dominated the practice of midwifery that aspects such as the effects of pregnancy on the cardio-vascular system were rarely considered. Generally, women were not seen by a doctor until difficulty was encountered in labour and thus opportunities for serial observation were few.

During the mid-nineteenth century there was a long controversy, mainly in France and Germany, about whether there was cardiac hypertrophy in pregnancy (Larcher 1859, Macdonald 1878). Larcher (1859) supported the concept of cardiac enlargement. His studies consisted of careful inspection and measurement of the heart in pregnant and puerperal women. However, his material consisted entirely of post-mortem hearts, often from women dying of sepsis or after exhausting labours and his findings may have been affected by the terminal illness. Considering the lack of suitable methods of study, it is not surprising that the argument could not be resolved.

The importance of heart disease as a cause of deterioration of health in pregnancy does not seem to have been well-recognised, although the ravages of acute rheumatism on the heart valves were well-known. Peter, in 1872, describes a French aristocrat who developed acute pulmonary oedema in the fifth month of her second pregnancy. He had attended her during a similar episode at the same stage in her first pregnancy, when spontaneous delivery of a dead foetus relieved her

respiratory distress. The recurrence led to his examining her heart when, to his surprise, he found evidence of rheumatic heart disease. With rest and supportive therapy the pregnancy continued successfully to term. His concept of the cardiac burden of pregnancy seems to have rested largely on the increased load due to the foetal circulation as he considered that the stage of pregnancy was significant - - - "c'est-à-dire, à une époque où le sang du foetus commence à avoire une certaine masse". Hunter (1774), however, a century earlier had been aware that the maternal and foetal circulations were separate. He illustrated the point in Plate 24 of his superb engravings of the human gravid uterus. By injection of wax he could fill the interstices of the placenta from either the uterine artery or vein but noted that none "passed into the branches of those vessels which compose the navel-string". To demonstrate the vessels within the substance of the placenta he had to inject the umbilical vessels. It is recorded that he taught his students that the placenta was composed of foetal and maternal parts "without any Vascular Communication between the two" (Cawley, 1778).

At about the same time as Peter's observation, Macdonald (1878) in Edinburgh, recognised the importance of rheumatic heart disease in pregnancy and wrote the first text-book in English on the subject. Reporting an alarming mortality rate of 61% in women with rheumatic heart disease in pregnancy, he made a systematic effort to evaluate the previous work and add his own observations concerning the physiological effect of pregnancy on the healthy as well as the diseased heart. Thus,

he declared, "it appears to be the fact that the pregnant condition modifies and affects the conditions of the collective blood vascular system in an all-important manner so that disease of lungs, kidneys etc. are greatly conditioned thereby". Only a primitive sphygmogram was available to record blood pressure since the method of auscultatory sphygmomanometry developed by Riva - Rocci and Korotkoff (see Pickering 1955 for an account of the development of blood pressure measurement) was not introduced until the turn of the century. Using the primitive sphygmogram available, consisting of apparatus to apply direct pressure over a pulse with a clockwork system of levers to record the pressure, Macdonald produced some remarkable arterial pulse records and observed that the pulse "tension" was high in late pregnancy and remained so in the early lying-in period. Mahomed (1874) had described similar findings. Macdonald (1878) also studied the post-mortem appearances in eclampsia and referred to "extreme anaemia of the cerebral centres and the effect of impure blood on them".

Thereafter, physical methods of investigating the heart with the polygraph, sphygmograph, stethoscope and electrocardiograph invaded the scene to such an extent that the functional capacity of the patient was apt to be neglected. Before the range of normality of these physical methods of investigation had been established, the undue attention paid to small variations in the findings led Mackenzie (1921) to warn against causing unnecessary alarm to pregnant women on account of presumed abnormal signs, possibly of no significance. He declared

that his text-book on Heart Disease and Pregnancy (1921) was an attempt to counteract the contemporary text-books where the views expressed were not so recent as those propounded by Macdonald in 1878. He warned that more harm might accrue by provoking over-anxiety than by omitting to detect organic disease. Later, Bramwell and Longson in their book on Heart Disease and Pregnancy (1938) open with the statement that most heart disease in pregnancy is imaginary. No description is given of the effect of pregnancy on the cardio-vascular system of the normal woman.

Interest in this aspect was, however, intense in some centres and Jensen (1938) published an extremely comprehensive account of the current knowledge concerning the work of the heart, basal metabolism, blood volume, blood pressure, venous pressure, circulation time and oxygen utilisation in normal pregnant women.

During these observations of the cardio-vascular system in pregnancy little attention was paid to the peripheral circulation although as early as 1862 Raynaud, in describing a woman of 26 years who had digital vasospasm of the type described by him, stated:- "chose assez curieuse, sa disparition complète a toujours été notée par cette dame comme le premier indice d'une grossesse commençante". Even earlier, Denman (1782) made an indirect reference to the peripheral circulation when he offered the following advice for the management of the pregnant woman with insomnia:- "a towel dipped in cold water and wrapped round the hand, with one corner hanging over the edge of the

bed has many times been serviceable in procuring sleep by lessening the general heat of the body".

In 1904, Bacon produced a theory, quite unsupported by any direct observations, that in pregnancy a factor was produced stimulating vasodilatation of the splachnic area and vaso-constriction of the rest of the body. This view seems to have prevailed for many years. Later authors, (Jensen 1938, Abramson, Flachs and Fierst 1943) have attributed it to Huchard in 1910, but study of the reference quoted and of his other available writings (1899, 1908) does not confirm that he expressed this opinion.

CURRENT CONCEPTS OF GENERALIZED CARDIO-VASCULAR CHANGES IN PREGNANCY

Investigations in more recent years into the haemodynamics of pregnancy (Burwell, Strayhorn, Flickinger, Corlette, Bowerman and Kennedy 1938, Cohen and Thomson 1939, Bader, Bader, Rose and Brunwald 1955, Vorys, Hanusek and Ullery 1963) have generally dealt with the overall effect of pregnancy on the circulation. The aspects most studied include blood pressure, pulse rate, cardiac output, blood volume and oxygen utilisation. A summary of the main conclusions is set out below.

ARTERIAL BLOOD PRESSURE

Although the level of arterial blood pressure, especially when abnormal, has been the aspect of the cardio-vascular system in pregnancy most frequently observed, there have been varying reports concerning changes in blood pressure in normal women in pregnancy. Hare and Karn (1929) in a large and carefully conducted series reported a slight fall in both systolic and diastolic pressure until near term when there was a tendency for both to rise, while Henry (1936) found no change in systolic pressure but a slight relative rise in diastolic pressure near term. This latter finding seems to be the most consistent trend in the other studies (Landt and Benjamin 1936, Cohen and Thomson 1939, Burwell and Metcalfe 1958).

It is not surprising that there are discrepancies in observing changes which are relatively small since population-type studies of arterial blood pressure contain many inherent difficulties. Besides

true variations in arterial pressure in response to physical activity and emotional state there are inherent inaccuracies in the method of measurement. Both the size of the subject's arm and the contour of the pulse wave can affect the value obtained (Ragan and Bordley 1941) while age introduces another variation (Master, Dublin and Marks 1950). Sampling errors in obtaining a representative group from any population present difficulties which have been discussed by Pickering (1955). Further, in addition to the varying accuracy of individual instruments, there are systematic and unpredictable errors in recording, an aspect recently reviewed by Rose, Holland and Crowley (1964). Thus, one observer may habitually read higher or lower than another while some have a preference for certain terminal digits. This point was observed by Janeway in 1913 when he detected a preference for a terminal 0 recording in a large personal series of blood pressure recordings. There may also be prejudice for or against particular values especially when a reading, for example 140/90 mm.Hg., represents a division between groups. A further basic difficulty in pregnancy lies in the definition of normal pregnancy since any large series will tend to include a number of patients with mild toxaemia.

On review of the older literature, including some of the studies concerning blood pressure in normal pregnancy referred to above, Jensen (1938) stated: "I have been unable to find convincing evidence that the blood pressure does not, in late pregnancy, exhibit a tendency to approach the upper limits of normal". And later, "Whether it exceeds

the upper limits of normal depends somewhat upon what those limits are set to be". There seems to be nothing in the subsequent literature to add to or alter this opinion.

PULSE RATE

Even this simple measurement has provided varying results, the difficulty being to standardise the conditions. Many reports, some showing no increase in rate and others an increase unrelated to the stage of gestation, quoted by Jensen (1938) appeared before that of Burwell and his colleagues in 1938. The latter, however, is very widely quoted despite the fact that it was merely an incidental observation in some other studies and referred to only four patients, one of whom had rheumatic heart disease. Although an average increase occurred reaching a maximum of ten beats per minute at 28 - 32 weeks of pregnancy, one of the four subjects had a consistently lower pulse rate during pregnancy than ten days after delivery. So many of the other reports of pulse rate in pregnancy have been incidental to studies such as cardiac output determinations (Werko 1954, Bader et al. 1955) that patients cannot necessarily be regarded as being in a normal or "basal" state. Hytten and Leitch (1964), after analysing the available studies, conclude that there is an average increase of about fifteen beats per minute compared with the non-pregnant subject with no evidence of a fall in rate in late pregnancy. They consider that no longitudinal study under satisfactory conditions has yet been carried out.

CARDIAC OUTPUT

Despite the limitations of the early gas methods (Stander and Cadden 1932, Burwell et al. 1938) and the shortcomings of the early catheter studies (Palmer and Walker 1949, Hamilton 1949) where radiographic control was not used and values for arterial oxygen levels were assumed, most measurements agreed that there is an elevation of cardiac output in pregnancy. While subsequently confirmed by other workers (Werko 1954, Bader et al. 1955) also using cardiac catheterisation but including pulmonary artery samples, the extent and time of maximum increase is uncertain. The average of the findings of several series tends to show a maximum level at about 28 - 32 weeks of pregnancy and this view has widely prevailed. However, the pattern of change in relation to gestation varies widely between series. A disadvantage in most series is that the same patients have not been studied at different stages of the pregnancy. A recent study (Walters, MacGregor and Hills 1966) by a dye-dilution technique, using a photo-electric ear-piece with repeated determinations in a group of patients showed higher levels in the first trimester and again at 24 to 32 weeks of gestation compared with 14 to 24 weeks and after 32 weeks. The level found at term was not elevated compared with non-pregnant levels.

Measurements of cardiac output in all the quoted series were made in the supine position. However, it has long been recognised (Runge 1924, Burwell 1938) that there is a rise in venous pressure in the lower, compared with the upper limbs in pregnancy. Later authors

(Brigden, Howarth and Sharpey-Schafer 1950, Howard, Goodson and Mengert 1953) have shown that the rise in venous pressure in the lower limbs, presumed to be due to obstruction to the inferior vena cava, may be associated with the supine hypotensive syndrome in some women, a fall in femoral venous pressure, accompanied by relief of symptoms, occurring with alteration from the supine to the lateral position. Kerr, Scott and Samuel (1964) have further shown that this obstruction to the inferior vena cava occurs in all women and that there is a collateral circulation via the vertebral and hemiazygous plexus. The inadequacy of this latter system in some women probably accounts for a sufficient fall in venous return to cause hypotension. Veryn, Ullery and Hanusek (1961) have shown a substantial decrease in measurements of cardiac output in late pregnancy in the supine compared with the lateral position. This finding has been confirmed by Kerr (1965). It may well be, therefore, that cardiac output remains high towards term. Recent values obtained by Pyörälä (1966) although not serial, show no reduction in cardiac output at term compared with mid-pregnancy.

A few studies of cardiac output have been continued into the early puerperium. Burwell and his colleagues (1938) found a reduction two weeks after delivery compared with the level in pregnancy. Hamilton (1949) found the levels 4 to 14 days after delivery similar to non-pregnant, early pregnant and term levels, while Adams (1954) using a dye dilution technique found an increase of about 30% in the early puerperium compared with term pregnancy.

The wide variation in actual levels of cardiac output, although reduced by expression of the result in relation to body size, makes an estimate of the quantitative increase difficult. However, study of the published work suggests that cardiac output, at its highest average level, is about 6 litres per minute compared with about 4 - 5 litres in the non-pregnant woman.

Since the relative increase in cardiac output, even allowing for the wide variation in the actual amount is greater than the increase in pulse rate, it follows that stroke output in pregnancy must be increased.

PERIPHERAL RESISTANCE

It also follows that, since there is an increase in cardiac output in normal pregnancy with very little change in blood pressure, the overall peripheral resistance must be reduced. Bader and his colleagues (1955) using their own measurements of systemic arterial pressure and cardiac output show a rise in peripheral resistance from 20 weeks of pregnancy to term; a finding resulting from the measured fall in cardiac output towards term. Mendelson (1960) illustrates the point with a chart showing a decrease from the onset of pregnancy to 20 weeks and a rise thereafter to term, the levels at the beginning and end of the pregnancy being similar. The source of the data used is not stated.

Pyörälä (1966) compared three groups of women at different stages of pregnancy (fifth month to term) with a group of non-pregnant control

subjects and found a reduction in overall peripheral resistance in pregnancy. This reduction was greater in mid-pregnancy than near term. The findings were calculated from his own measurements made in the left lateral position. The blood pressure was determined by auscultation and the cardiac output by means of dye dilution and a photo-electric ear-piece.

OXYGEN CONSUMPTION

While oxygen consumption rises in pregnancy, the increase, of about 10%, by term (Bader et al. 1955) is less than the increase in cardiac output. As expected from this difference, arterio-venous oxygen difference is lower in pregnancy (Burwell et al. 1938, Palmer and Walker 1949, Bader et al. 1955). All these workers have shown an increase in oxygen arterio-venous difference towards term.

VENOUS PRESSURE

While remaining unchanged in the upper limb, there is a progressive rise in femoral pressure during pregnancy (Burwell 1938, McLennan 1943). There is no increase in right atrial pressure (Hamilton 1949) or right ventricular pressure (Bader et al. 1955). This difference indicates obstruction between the two points, occurring, as discussed above, at the inferior vena cava. It is also probable that some of the increase in femoral pressure is due to relatively high pressure in the uterine veins but direct measurement of this is difficult.

BLOOD VOLUME

Changes in blood volume in pregnancy have been the aspect of haemodynamics in pregnancy, most frequently studied under experimental conditions (Thomson, Hirsheimer, Gibson and Evans 1938, Caton, Roby, Reid, Caswell, Maletskos, Flubarty and Gibson 1951, Adams 1954, Pritchard, Wiggens and Dickey 1960, Pritchard 1965, Rovinsky and Jaffin 1965). While differing methods have been used with considerable quantitative variation in the findings, there is no doubt that both plasma and red cell volumes increase in pregnancy. The increase in plasma volume appears to be about 50% at its maximum, the volume increasing from an average level of 2600 ml to 3900 ml. Most of the published series show a decrease just before term compared with 36 weeks but this observation is not consistent in all series, McLennan and Thouin (1948), for instance, finding no decrease. Statzer's results (1959) do not show a fall though he does not specifically discuss the point. Pritchard (1965) in a recent study found no distinct decrease in late pregnancy but in fact observed a slight rise right up to term. As with cardiac output estimations, the supine position in late pregnancy may influence the findings.

Changes in red cell volume seem to be more variable and are necessarily influenced by the occurrence of varying degrees of anaemia. It seems to be undoubted that an increase occurs, probably of the order of 250 - 400 ml. (Caton et al. 1951, Pritchard et al. 1960). This represents an increase in red cell volume of about 18 - 30% (Hytten and

Leitch 1964), which is relatively less than the corresponding increase in plasma volume. There is no convincing evidence of a reduction before term and where serial studies have been carried out the increase during pregnancy seems to be progressive.

This large increase in blood volume is one of the fundamental changes in the haemodynamic system in pregnancy and its extent, varying widely between patients (McLennan and Thouin 1948, Pritchard 1965), may well determine the magnitude of other cardio-vascular changes in a particular subject. The averaged results suggest a relative increase of blood volume compared with cardiac output, implying pooling of blood but simultaneous measurements would be required to elucidate this.

MECHANISM OF CARDIO-VASCULAR CHANGES

The basic factors controlling these haemodynamic changes in pregnancy are not known. Were the increased cardiac output solely the result of the increased metabolic demands of pregnancy, we would expect a proportional increase in oxygen consumption. However, as it is much less than the increase in cardiac output, it cannot be the primary stimulating factor.

The maintenance of blood pressure within relatively narrow limits despite the large variations in vascular bed and blood volume has been attributed to increased neurogenic tone (Brust, Assali and Ferris 1948). These workers found a difference in response to both high spinal anaesthesia and injection of the autonomic blocking agent, tetra-ethyl ammonium chloride (T.E.A.C.) in healthy women in late pregnancy compared

with non-pregnant women. In the pregnant group, there was a profound fall in blood pressure while in the non-pregnant group there was only a slight fall. It was presumed that the vasodilatation resulting from release of autonomic tone meant that there was a greater degree of neurogenic tone before the block. Since, turning the patient on her side or raising her legs to 90° relieved the hypotension, while preliminary occlusion of the legs prevented it, pooling of blood was considered to be an important result of autonomic blockade in late pregnancy (Assali and Prystowski 1950). Considering this undoubted mechanical effect of the gravid uterus in late pregnancy, pooling of blood could occur, not only in the legs but in the entire lower half of the body, thus enormously reducing venous return and readily inducing hypotension. Therefore, the interpretation by Assali and his colleagues that a greater quantitative effect of autonomic blockade on blood pooling implies a greater degree of neurogenic vasoconstrictor tone before the block is not necessarily wholly justified.

In 1938, Burwell suggested that the cardio-vascular changes in pregnancy resembled the changes occurring with arterio-venous fistulae. In such patients increase in heart rate, pulse pressure, cardiac output and blood volume occur, the magnitude of the changes bearing some relation to the size of the fistula (Reid 1925, Cohen, Edholm, Howarth, McMichael and Sharpey-Schafer 1948). Burwell (1938) considered that the structure of the placenta was such that it could be acting as an arterio-venous fistula although the fall in cardiac output as measured

near term was a serious drawback to the theory. This concept was further elaborated by McGaughey (1952) who, with singular lack of evidence, declared that towards term the increasing tortuosity of the chorionic villi and narrowing of the maternal vessels due to uterine stretching as a result of increasing uterine contents obliterates the arterio-venous fistula effect in late pregnancy. He postulated further that near term, the placental site reverses its haemodynamic effect and becomes an area of increased resistance leading on logically in some instances to pre-eclampsia. However, the fact that resting intra-amniotic pressure rises only very slightly in pregnancy and is generally less than 15 cms of water near term (Alvarez and Caldeyro 1950) is incompatible with this theory. Further, while it is appreciated that there is no capillary system in the placental site, there is much tortuosity of the uterine arterioles. More recent work (Ramsey 1959), has shown that the placental flow pattern is pulsatile, intermittent and greatly impeded during the normal contractions of the uterus in pregnancy (Caldeyro-Barcia 1957), suggesting that the overall resistance to flow is not inconsiderable. Details of the changes of uterine blood flow during the course of normal human pregnancy are not well-established but where measurements have been made there is no evidence of a reduction at term (Metcalfe, Romney, Ramsey, Reid and Burwell 1955).

Another objection to the concept of a shunt mechanism being the main determinant of the haemodynamic changes in pregnancy is that the central arterio-venous oxygen difference increases by about 1 volume %

in late compared with mid-pregnancy (Bader et al. 1955). It is inconceivable that a change of this magnitude could be due to a reduction in uterine blood flow in late pregnancy and it is clear that other organs and areas of the body must be involved in altering the central venous oxygenation.

While it is undoubted that the placental site is a relatively low resistance segment of the circulation in pregnancy the parallel with an isolated arterio-venous fistula has, at best, great limitations. The uterus is clearly not the only area of the body undergoing profound changes in pregnancy. The extent to which other regions contribute to the decreased peripheral resistance depends on the study of regional blood flow and its variations with the stage of gestation. Our knowledge of this in the healthy pregnant woman is limited.

REGIONAL HAEMODYNAMIC CHANGES IN PREGNANCY

UTERINE BLOOD FLOW

The most obvious region of increased blood flow in pregnancy is the uterus. Available methods of measurement contain inherent inaccuracies and grave technical difficulties arise in their application to human subjects. It is not, therefore, surprising that the changes which have been found show considerable variation. Using an electromagnetic flowmeter directly on uterine vessels at hysterotomy, Assali, Rauramo and Peltonen (1960) found flow to increase from about 50 ml per minute at 10 weeks of pregnancy to about 150 ml per minute between 24 and 28 weeks. The method is not reasonably applicable to later pregnancy with a viable foetus and other less direct methods have had to be used. Assali, Douglass, Baird and Nicolson (1953) have used the Fick principle employing nitrous oxide in women near term and have estimated the flow to be about 750 ml per minute. They assumed equilibration of nitrous oxide between the maternal blood and uterine contents after 30 minutes. However, Metcalfe, Romney, Ramsey, Reid and Burwell (1955) have shown that one hour at least is required and that this assumption of Assali and his co-workers would tend to overestimate flow. To obviate this difficulty, Metcalfe's group, also using the Fick principle and nitrous oxide, measured the gas concentration in liquor, uterus and baby at the time of blood sampling and delivery. Their estimate of uterine blood flow is about 500 ml per minute but there is a very wide variation in the individual readings. One difficulty

of the method is that uterine vein blood drains not only the placental site but also other portions of the genital tract and there may be asymmetry depending on the placental site. Also, estimation of the nitrous oxide in the uterus and foetus is necessarily approximate. An indirect method of ^{24}Na injection into the chorio-decidual space has also been used (Browne and Veall 1953), but requires the assumption of a constant and estimated volume of the placental pool of blood. A flow of about 500 ml per minute is estimated near term. Despite the short-comings of both these latter studies, the agreement in findings makes this figure the currently accepted estimate of average uterine blood flow near term.

RENAL BLOOD FLOW

Studies of renal plasma flow in pregnancy have mostly depended on Para-amino hippurate clearance (PAH) (Bucht 1951, Levitt 1957, Sims and Krantz 1958, Werko 1961, and Chesley 1963, 1965). There is general agreement that there is a rise in renal plasma flow of about 25% occurring early in pregnancy. Most series have shown this increase sustained until the last few weeks of pregnancy when there has been a reduction in the measurement, in some cases approaching non-pregnant levels. However, Pritchard, Barnes and Bright (1955) and Chesley and Sloan (1964) have demonstrated a reduction in both renal blood flow and renal function in late pregnancy in the supine compared with the lateral position. The latter author estimates that in the last weeks of pregnancy, measurements of renal plasma flow are probably under-estimating

the true value by about 20 - 25%. It is possible, therefore, that there is no true fall in renal plasma flow in late pregnancy.

LIVER BLOOD FLOW

Using the Fick principle with bromsulphthalein and direct catheterisation of the inferior vena cava, Munnell and Taylor (1947) showed no change in liver blood flow in pregnancy compared with non-pregnant control subjects. The relative proportion of blood volume circulating through the liver was therefore assumed to be reduced.

CEREBRAL BLOOD FLOW

McCall (1949), using nitrous oxide and the Fick principle, showed no change in cerebral blood flow in pregnancy compared with non-pregnant control subjects.

OTHER REGIONS

The breasts may be presumed to have an increased blood supply in pregnancy but there do not seem to be any quantitative estimates. Regions such as the thyroid gland, vagina and perineal tissues may well have an increased blood supply but the total amount involved is relatively small.

SUMMARY OF HAEMODYNAMIC CHANGES IN PREGNANCY

Consideration of the data discussed in these sections suggests that in mid to late pregnancy there is, on average, an increase of about a litre and a half of blood. Most or all of this increase is pumped through the heart each minute with a slight increase in heart rate and no substantial alteration in blood pressure.

The flow through the uterus of about 500 ml per minute and the increased blood flow of about 300 ml per minute through the kidneys represents about half the increase in cardiac output. The remaining increase is not equally distributed throughout the body. The extent to which areas other than the uterus contribute to the decreased resistance is not known. The mechanism controlling the varying regional distribution of the increased cardiac output is also unknown.

PERIPHERAL CIRCULATION IN PREGNANCY

Relatively little of the published work on the circulatory changes in pregnancy refers to the peripheral circulation.

Widespread systemic vasodilatation has been assumed (Levitt 1957). Werko (1954) states: "The skin blood flow and renal blood flow increase" while Winner (1965) in a review article estimates an increase of 300 - 500 ml of blood to the extremities in mid and late pregnancy.

The evidence on which these statements are based is scanty and conflicting.

PREVIOUS STUDIES

The first systematic study of the peripheral circulation in pregnancy was made by Abramson, Flachs and Fierst in 1943. Using venous occlusion plethysmography, they measured hand, forearm and leg blood flow on several occasions in the last two trimesters of pregnancy and in the puerperium in 12 healthy women and 1 with mitral stenosis. They compared the findings with those in a group of non-pregnant women. They do not state whether the "leg" measurements include or exclude the foot, but from the illustrations in a subsequently published book (Abramson 1944) where the results are also discussed, it is clear that only the calf segment was measured. These authors found that the blood flow in the forearm and calf remained within normal limits at the stages studied. There was about a threefold increase in hand flow between 20 weeks and late pregnancy. An immediate fall in hand flow after delivery was not observed although only four measurements were made

in the first three weeks of the puerperium in the seven subjects whose hand flow in pregnancy was measured. It was concluded that the increased uterine blood flow in pregnancy was not obtained at the expense of the extremities; a view which, as stated in the historical introduction, had prevailed until then. However, the number of studies in each limb was few and the plethysmograph temperature used (32°C) would have caused some vaso-constriction in the forearm and calf segments (Barcroft and Edholm 1943).

Subsequently, further studies were reported (Burt 1949, 1950). Hand and forearm blood flow were again measured by venous occlusion plethysmography. A progressive rise in hand flow was found, a value of seven times the non-pregnant level being reached in the last month of pregnancy. Forearm flow was studied on 8 patients once in late pregnancy and again on one occasion at times varying from 1 to 10 weeks in the puerperium. The mean values obtained were 3.51 ml/100 ml tissue/min in pregnancy compared with 2.54 ml in the puerperium. The plethysmograph temperature is not stated and the room temperature varied between 15 and 22.5°C. Although the difference in the two values is claimed as an increase, statistical analysis does not support the statement that there is any difference ($t = 1.7$. $P > 0.1$). Reflex vaso-dilatation by immersion of the feet in a water-bath at 43.5°C showed an increase of forearm flow to 5.3 ml/100 ml tissue/min in pregnancy compared with 3.3 ml in a group of 6 non-pregnant women whose forearm flow before heating was 2.06 ml. This increase in both

groups is small compared with the increase in forearm flow found in healthy non-pregnant subjects by Barcroft, Bonnar and Edholm (1947) using a similar technique.

A study was also made of nail-fold temperature (Burt 1949). This showed a substantial rise in temperature in the fingers in pregnancy even when the subject was kept in a cool environment. It was noted that finger skin temperature was still elevated in the puerperium although at a lower level than in late pregnancy. A corresponding study in toes showed a rise from mid-pregnancy to term although to a lesser extent. However, skin temperature is influenced by factors such as humidity, metabolism of underlying tissues and pooling of blood. Hence, nail fold temperature gives an unreliable estimate of the rate of blood flow. Local stagnation on the venous side could well be an important variable especially in the lower limb in pregnancy. Further, at higher rates of blood flow skin temperature increases relatively less for a further increment in flow thus making moderate additional increases impossible to detect. It is also recognised that the nail bed is singularly rich in arterio-venous anastomoses and is not representative of other regions.

In a later study (Herbert, Banner and Wakim 1958) forearm and leg blood flow were measured. It is not stated in this paper, either, whether the leg included the foot as well as the calf. In non-pregnant control subjects forearm flow was 4.56 ml/100 ml tissue/min. In pregnant subjects there was a fall in forearm flow in early pregnancy

followed by a rise in mid and late pregnancy, the level at 36 weeks of pregnancy being 8.73 ml; an increase of 91% compared with the non-pregnant control subjects. In the "leg", the level of blood flow at 36 weeks of pregnancy was 3.18 ml compared with 1.89 ml in the non-pregnant group; an increase of 70%. There was a decrease just before term. No figures of actual levels obtained other than those quoted are given. The magnitude of the variations claimed and the range between subjects are not stated. Venous occlusion plethysmography was used but there is no description of the apparatus used or any details of the procedure. Neither the room temperature nor that of water surrounding the plethysmograph at the time of the studies is stated. Skin temperature measurements were also made in this study, a rise in temperature in both fingers and toes being found.

Another study (Mendlowitz, Altchek and Naftchi 1958), compared the digital blood flow in a group of normotensive women in the third trimester of pregnancy with a group of non-pregnant women. Each subject was studied on one occasion. The mean values found were 0.29 cm^3/cm^2 skin/min in the pregnant women compared with 0.20 cm^3/cm^2 skin/min in the non-pregnant group. A calorimetric method was used. Calculation of actual blood flow from calorimetric measurements depends on the assumption of the temperature of the arriving and departing blood. The use of body core and water calorimeter temperatures gives a minimal possible blood flow for the measured heat exchange (Greenfield and Shepherd 1950), but the actual flow may exceed the calculated value (Greenfield, Whitney and Mowbray 1963).

SUMMARY OF PREVIOUS WORK ON PERIPHERAL CIRCULATION IN PREGNANCY

These published studies show a rise in hand blood flow in pregnancy but its magnitude and relation to the duration of pregnancy and delivery are uncertain. There is disagreement concerning forearm blood flow; the calf has been inadequately studied and no measurements of foot blood flow have been made.

In view of the uncertainty of the true nature of the changes in the peripheral circulation in pregnancy, a comparative study was undertaken of hand, foot, forearm and calf blood flow in a group of healthy women during pregnancy and the puerperium. While this study was in progress, a further report concerning forearm blood flow was published (Spetz 1964) showing a progressive increase in forearm blood flow during pregnancy, the level at term being seven times that found in early pregnancy. There are a number of important differences between his technique and that used in the present series. Hence, appraisal of his method and findings and comparison with the present study is made after the presentation of results.

PRESENT STUDY - SECTION I

LIMB BLOOD FLOW IN NORMOTENSIVE AND HYPERTENSIVE PREGNANCY

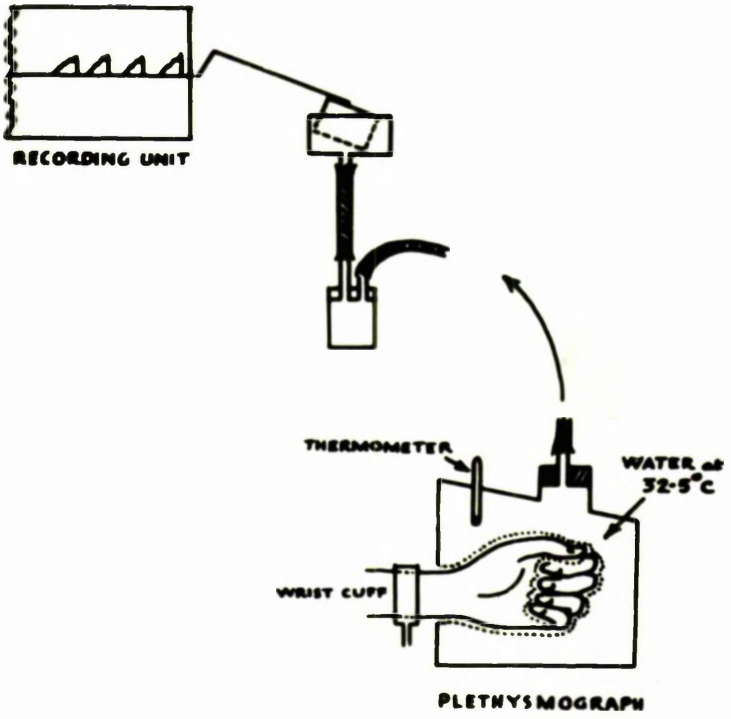


Fig. 1. Diagram of plethysmographic apparatus used for the measurement of hand blood flow.

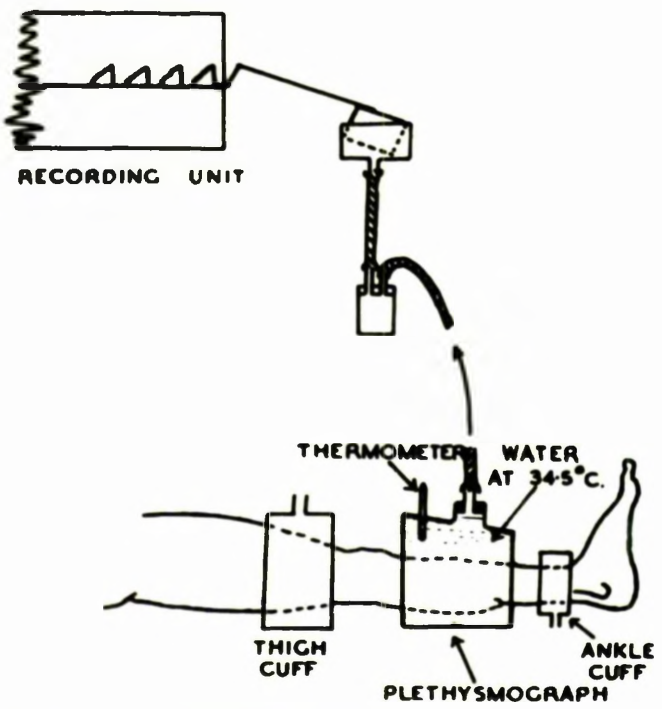


Fig. 2. Diagram of plethysmographic apparatus used for the measurement of calf blood flow.

METHOD

In this study, venous occlusion plethysmography has been the method used for the measurement of limb blood flow. This principle of measuring the rate of increase of limb volume during brief arrest of venous return has gradually developed from the mid-nineteenth century. Marey recounts in his book "La Circulation du Sang" published in 1881 how several French physiologists had, over the preceeding forty years, devised enclosed water-filled containers where the rhythmic volume changes in a limb due to arterial pulsations were recorded. He further describes how Francois-Franck obtained "accroissement de volume de la main sous l'influence de la compression des veines" demonstrating immediate reduction in swelling of the hand on release of the compression. In 1905, Brodie and Russell described their application of the principle to measure renal blood flow in dogs. Methods of estimating blood flow used previously had all interfered with normal circulation. Their comparison with direct measurements of flow showed a good co-relation. By 1909, Hewlett and Van Zwaluwenburg had further adapted the principle to make quantitative measurements of blood flow in the extremities of man.

Since then, this method has been used extensively to study the physiology of the circulation in the limbs and details of the technique are provided by Barcroft and Swan (1953). Essentially, using water-filled plethysmographs, the procedure involves the application of a closely fitting rubber sleeve (in the hand, a glove) to the segment under study. This is surrounded by a rigid, metal container. A thick,

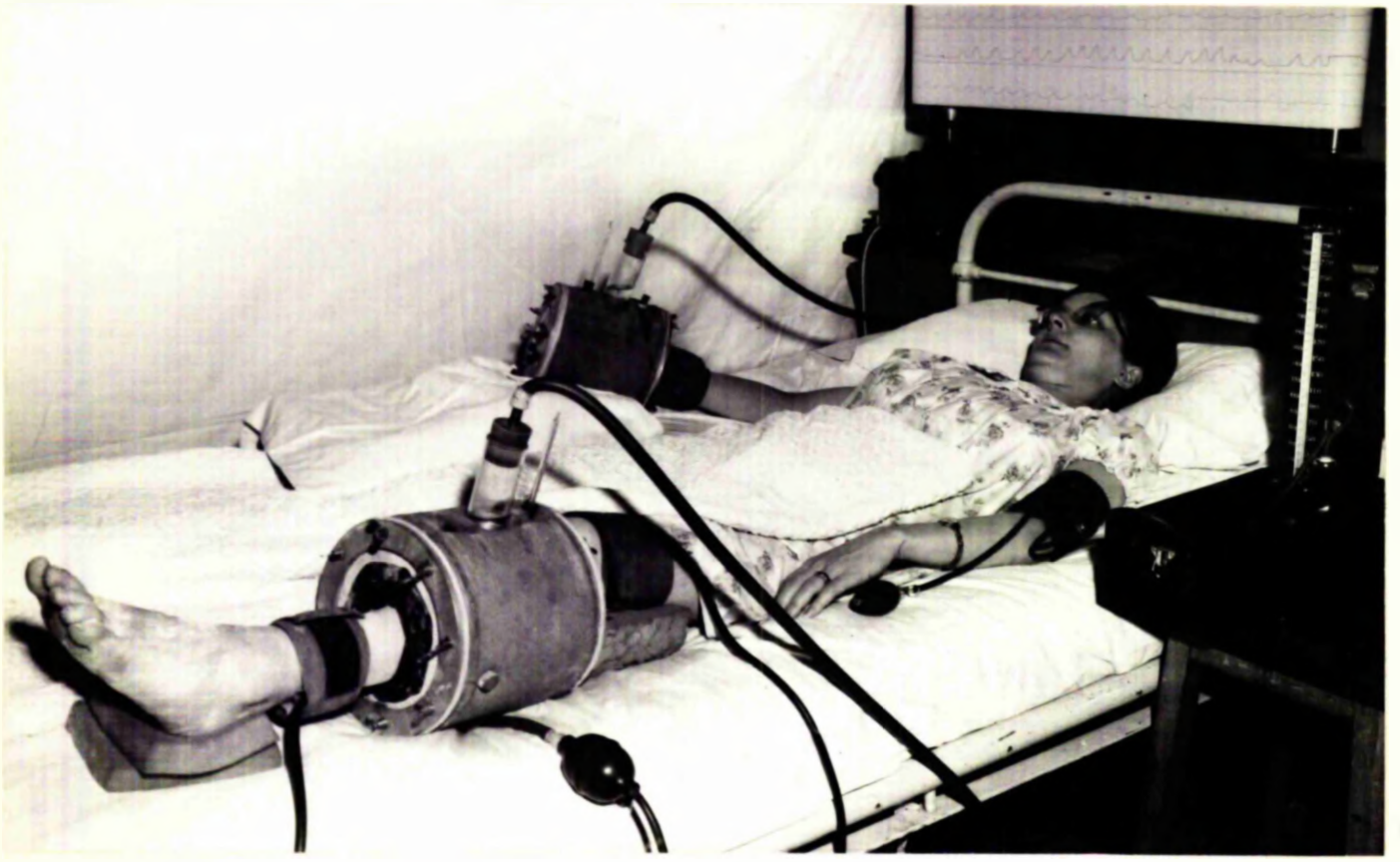


Fig. 3. Recumbent patient with hand and calf plethysmograph in position. Proximal venous occlusion cuffs are in position for both segments. For the calf there is also an arterial occlusion cuff. Recording apparatus in background.

rubber diaphragm attached to the end of the sleeve is fixed to the metal plethysmograph by metal plates and wing nuts to form a water-tight space between the sleeve and plethysmograph. A vertical column provides access for initial filling with water and for recording changes in the water level. The water temperature is recorded through an adjacent opening. Fig. 1 is a diagrammatic representation of the apparatus for the measurement of hand blood flow and Fig. 2 shows that for the calf. When the venous return from the segment under study is arrested, by an inflatable cuff immediately proximal to the plethysmograph, the volume of the enclosed segment increases. The increase in volume is transmitted, by the water surrounding the segment, to an air column connecting the plethysmograph to the recording system. This consists of a water-filled volume displacement recorder with a light-weight pen writing on a standard kymograph (Palmer). The apparatus is calibrated by the injection of air from a syringe, which forms part of the system. The displacement of the pen by a known volume is recorded. Fig. 3 shows the apparatus assembled for hand and calf blood flow measurement.

For forearm and calf blood flow recordings, inflow of blood from the hand and foot respectively is prevented by the application of inflatable cuffs distal to the plethysmograph. These distal cuffs and the proximal ones to provide venous occlusion, are connected to air-filled reservoirs by a three-way tap so that inflation of either cuff to a predetermined pressure can be applied instantly.

The rate of arterial inflow is indicated by the slope recorded

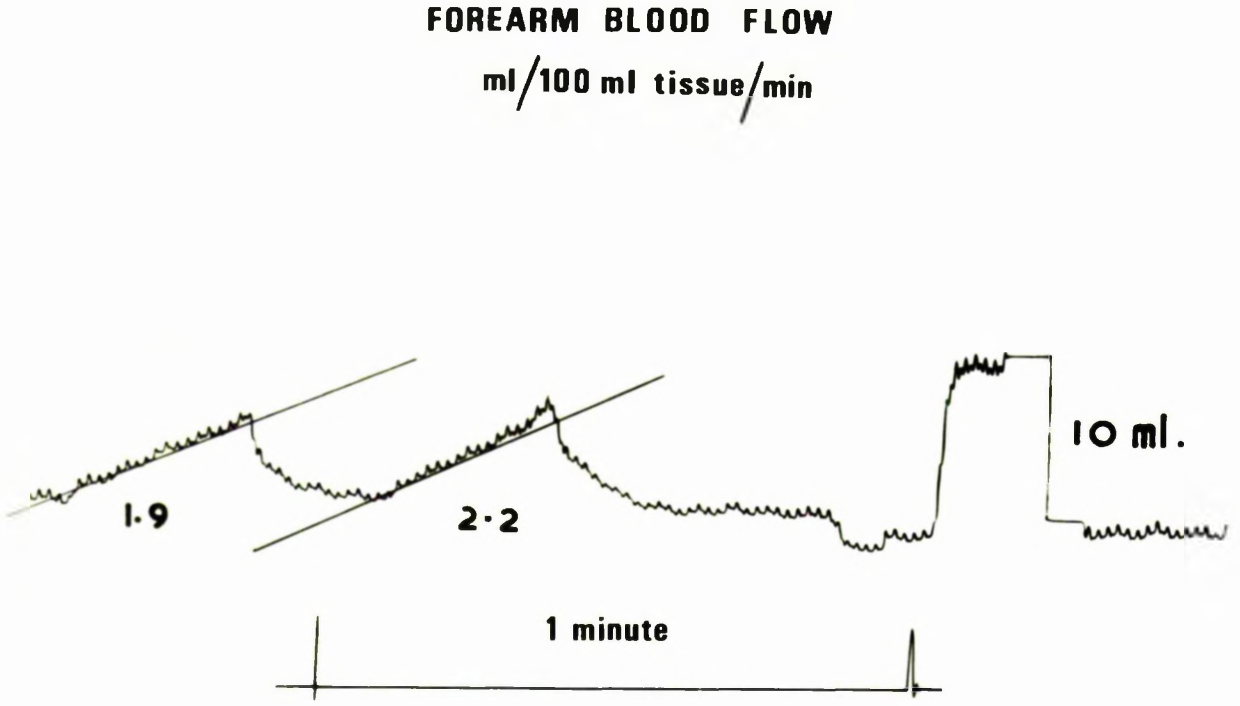


Fig. 4. Forearm blood flow recording to show calibration and calculation.

Time : 1 minute = 12 cms.
Calibration of pen : 10 ml = 3.5 cms.
Volume of forearm : 730 ml

For 1st. venous occlusion :
Slope = 4.9 cms. in 1 min.
≡ 14.0 ml in 1 min.
≡ 1.9 ml / 100 ml tissue / min.

For 2nd. venous occlusion :
Slope = 5.6 cms. in 1 min.
≡ 16.0 ml in 1 min.
≡ 2.2 ml / 100 ml tissue / min.

by the pen during venous occlusion. Fig. 4 shows a short period of forearm blood flow recording. The speed of the drum is measured in cms per min and the recording pen is calibrated in cms per ml. The volume increase for each venous occlusion can then be calculated.

In the hand and foot, blood flow through the skin predominates and total hand or foot blood flow reflects mainly changes in skin blood flow. In the forearm and calf, both muscle and skin can make a major contribution and changes in total forearm or calf blood flow may reflect changes in either skin or muscle or both.

While the fundamental technique has long been established, many studies have been carried out in recent years to evaluate possible fallacies or inaccuracies. Since the validity of the recording of the arterial inflow to a region obtains only if certain assumptions are tenable, it is important to consider these.

1) <u>The veins must be completely occluded</u>

This point has been studied in several ways. Tissue pressure at varying depths with an occlusion cuff applied has shown that all collapsible veins are occluded by a pressure of 50 mm Hg (Landowne and Katz 1942). Beyond this pressure, the same inflow is recorded within a wide range of occluding pressures (Greenfield and Patterson 1954). More direct evidence was obtained by Formal and Doyle (1957) who injected ^{131}I human serum albumin into a hand vein while applying a venous occlusion cuff. No leakage beyond the cuff occurred until the venous pressure approached the occluding one.

2) The application of the occluding cuff and rising venous pressure must not interfere with arterial inflow

That it is not reduced by the actual application of the cuff was shown by Wilkins and Bradley (1946) while Formel and Doyle (1957) demonstrated that the rise in venous pressure does not reduce arterial inflow. Further, in dogs, they found that direct measurements of arterial inflow corresponded closely to that obtained by venous occlusion plethysmography, as used on a human limb.

3) The above conditions must obtain for sufficient time to allow measurement

After the first few seconds, the increase in volume of the part may become asymptotic instead of linear showing cuff leakage. Consequently, only the initial linear part after occlusion should be used for calculation (Barcroft and Swan 1953, Greenfield and Patterson 1954).

4) Any artefact present must be easily observed and evaluated

Application of the cuffs often causes some displacement of tissue into the region under study. Re-adjustment may eliminate this.

5) Venous return from distal segments not being measured must be prevented

During the measurement of non-terminal limb segments, for example the forearm and calf, it is necessary to prevent return of blood from the distal segment during the recording of arterial inflow (Grant and Pearson 1938). Distal supra-systolic pressure has generally been used. This causes the immediate entry of some blood into the segment under

study, the increased volume subsiding in 10 to 15 secs. Kerslake (1949) has shown that the rate of apparent inflow to the forearm fluctuates after application of the wrist cuff and venous occlusion readings are valid only after the first minute. Graf (1964) has demonstrated a 6% increase in brachial artery pressure after distal occlusion and recommends occlusion to diastolic levels to exclude venous return only. There is doubt, however, of the efficiency of this procedure (Kerslake 1949) and, although used in Sweden, the modification has not been adopted in laboratories in the United Kingdom.

PLAN AND PROCEDURE OF PRESENT STUDY

Limb blood flow was measured in both healthy women and those with certain abnormalities. Patients for study were selected from the ante-natal clinic and ward. The total group comprised apparently healthy primigravidae and multigravidae with single and multiple pregnancy, women with known hypertension before pregnancy, women with a history of toxaemia of pregnancy, those who developed hypertension in pregnancy and a few with systemic non-hypertensive disorders. Clinical details of the entire group of pregnant women studied in the present thesis are given in Tables A to L in the Appendix. Each number refers to a different patient and this reference number is maintained throughout the presentation of results. Sub-division of the patients has been carried out according to diagnostic criteria discussed in the relevant sections. Allocation to the respective group was made after delivery and in some instances could be made only after the blood pressure had been recorded some weeks after delivery. Thus, regardless of her actual state at the time a particular measurement was made, each subject appears in only one group according to the final diagnosis.

The intended procedure was explained to each patient and only those willing to co-operate were studied. Measurements were made at least two hours after a meal, the patients being lightly clothed and comfortably supported (Fig. 3, opposite p. 32). Studies were made both on out-patients and those in the wards. In most patients not more

than two limb segments were studied at a single session. Comparison with a group of non-pregnant women has not been made since many patients were studied serially in pregnancy and into the puerperium allowing comparative assessment of the findings. Women with varicose veins in early pregnancy were not selected for study but the development of mild varicosities during the course of pregnancy did not exclude them from the group.

The technique used was standardised to allow comparison of the results at different stages of the same pregnancy. The sources of error discussed in the previous section were avoided. Metal plethysmographs filled with water maintained at 32 ± 1°C for the hand, 34 ± 1°C for the foot and forearm and 35 ± 1°C for the calf were used. The ambient temperature was maintained at 20 ± 1°C (Barcroft and Swan 1953). Background noise was reduced to a minimum.

For venous occlusion, cuffs of 4.5 cms width were used except for the calf where a wider cuff of 6 cms was used to ensure adequate occlusion. The cuffs used to provide arterial occlusion at the wrist and ankle during forearm and calf measurements were 4.5 cms in width. Care was taken to position the cuffs close to the plethysmograph without causing an undue artefact due to tissue at occlusion being displaced into the segment being measured.

On the first occasion, sleeve size was selected to the nearest half-inch to provide as close a fit as possible to the limb. At subsequent visits, the side of the segment under study, the sleeve size

and the position of the limb were kept constant to enable comparison at different stages of pregnancy. The displacement volume of each segment studied was measured on each occasion.

During the initial 20 - 30 minutes of each test, the patient rested on the bed while the apparatus was assembled and any necessary adjustments made. Recordings were then made at 15 second intervals for at least 15 minutes. The occluding pressure was 10 mm below the diastolic blood pressure and was usually between 50 and 60 mm Hg. During measurements of the forearm and calf, distal arterial occlusion was maintained throughout by inflation of the cuff to a pressure 100 mm Hg above the systolic blood pressure. Arterial blood pressure was measured at the beginning and end of each session with recordings during the procedure when the pressure was labile or elevated. The diastolic level was taken at the fading of the Korotkoff sounds. Body temperature was checked orally with a clinical thermometer. The pulse rate was calculated from the plethysmographic tracing.

No studies were made during the first four days of the puerperium after a Caesarean section, since it has been shown that forearm blood flow is reduced following major surgical procedures (Ginsburg 1959). Similarly, no measurements were made within four days of a forceps delivery, if general anaesthesia had been used. Puerperal studies were also omitted in those with puerperal pyrexia or where the oral temperature was found to be 99°F or above at the time of limb flow recording.

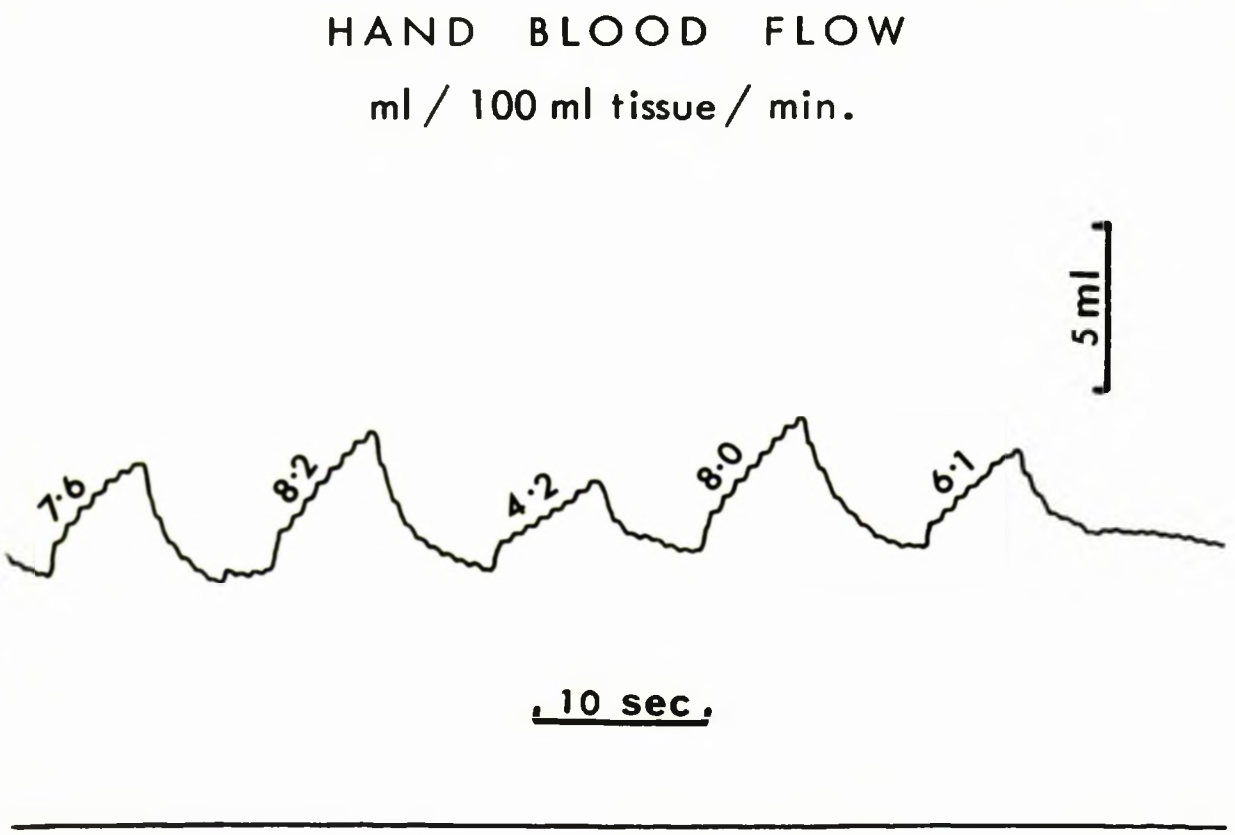


Fig. 5. Segment of hand blood flow showing spontaneous variation in flow over a period of 1 minute.

CALCULATION AND PRESENTATION OF RESULTS

During a particular limb blood flow measurement, the speed of the drum and the calibration of the pen were kept constant and were measured. The volume increase per minute could then be calculated for each venous occlusion. Division, by the volume in 100 ml, of the exact segment in the plethysmograph enabled limb blood flow to be expressed in units of ml blood/100 ml tissue/minute. Except where indicated otherwise, all limb blood flow recordings throughout this study are expressed thus (see Fig. 4).

To calculate the limb blood flow for a particular occasion, the readings obtained over the first few minutes were not included, the mean value being derived from readings obtained over a period of at least ten minutes. Consecutive flow recordings were used except for omissions related to any movement or obvious disturbance of the patient. In the hand and foot, a longer period of recording was generally taken to obtain the average value as there is considerable spontaneous variation in blood flow to the hand (Cooper, Cross, Greenfield, Hamilton and Scarborough 1949, Greenfield, Shepherd and Whelan 1951) and foot (Allwood and Burry 1954). Fig. 5 shows variable hand blood flow over a short period. A true value is therefore obtained only by taking the average of a large number of observations.

The values obtained were then sub-divided according to the limb and the stage of gestation. The tabulated results for each limb within each diagnostic group are given as the results are discussed. Figures

illustrating the main points are inserted at the appropriate place in the text.

INTERPRETATION OF LIMB FLOW RECORDINGS

In assessing the importance of changes in limb blow flow, the variations occurring normally must be considered. Precise limits of blood flow for different limb segments, as measured by plethysmography have not, to the author's knowledge, been strictly defined. Variations in environmental conditions are associated with differences in the absolute levels, which may invalidate comparisons between series. Further, not only do spontaneous variations occur but the extent varies with the temperature, being greater at intermediate temperatures (Cooper et al. 1949). A difference of as much as 30% may be found in blood flow simultaneously measured in normal contralateral forearms (Wilkins and Eichna 1941). The population studied may affect not only the absolute levels obtained but also the variability. Thus, Brown, Hatcher and Page (1953) found a mean forearm blood flow of 5.4 ± 0.18 ml/100 ml/min in a group of Eskimos compared with a value of 3.1 ± 0.15 ml/100 ml/min in Canadian medical students in identical conditions. Cooper, Edholm and Mottram (1955) found that forearm blood flow may vary considerably from day to day even with the subject at rest. However, although we cannot base any interpretation on small changes in individual limb blood flow recordings, mean values for a number of subjects show a fair measure of agreement between series provided the conditions are comparable.

Examples of resting limb flow measurements obtained in healthy subjects in other studies, using a similar technique and comparable conditions, are given below. All values are expressed in ml blood/100 ml tissue/minute.

Segment	Mean Value	Range (where given)	Author
Hand	5	-	Barcroft and Edholm 1945
	3.5	1.2 - 5.3	Hoobler et al. 1949
Foot	2.04	0.5 - 4.4	Hoobler et al. 1949
	3.5	1.0 - 6.7	Allwood 1958
Forearm	2.5	-	Barcroft and Edholm 1945
	3.1	-	Brown et al. 1953
Calf	-	1.4 - 6.5	Wilkins and Eichna 1941
	2.1	0.8 - 4.9	Allwood 1958

RESULTS - NORMOTENSIVE HEALTHY WOMEN WITH A SINGLE PREGNANCY

Clinical details of the 52 women in this group are given in Table A in the Appendix. No significant complication of pregnancy was present although induction of labour was carried out in four women on account of post-maturity and in one for a breech presentation. Caesarean section was carried out in one patient on account of a contracted pelvis and in two because of failure to progress in labour. Four patients had forceps deliveries. No patient who had a post-partum haemorrhage has been included in the analysis. All the babies survived except one (patient 19) where a forceps delivery was performed for foetal distress but the baby died within 24 hours of delivery. The average weight of the babies was 7 lb. 4 oz. As shown in Table A, selection of patients was made to avoid any seasonal bias.

The results of each limb studied are recorded separately. For each limb, the regression of the slope of the duration of gestation - mean limb blood flow line - was examined by means of analysis of variance. Values measured before the fifteenth week were excluded from this analysis since the studies before this had covered more than a four week period of gestation and further, this group was composed, almost entirely, of patients studied for the first time by this technique and therefore the values could have been influenced by initial apprehension. Measurements from 39 weeks to delivery were plotted at 40 weeks. The results between 15 and 40 weeks were grouped into periods of four weeks and co-related with time.

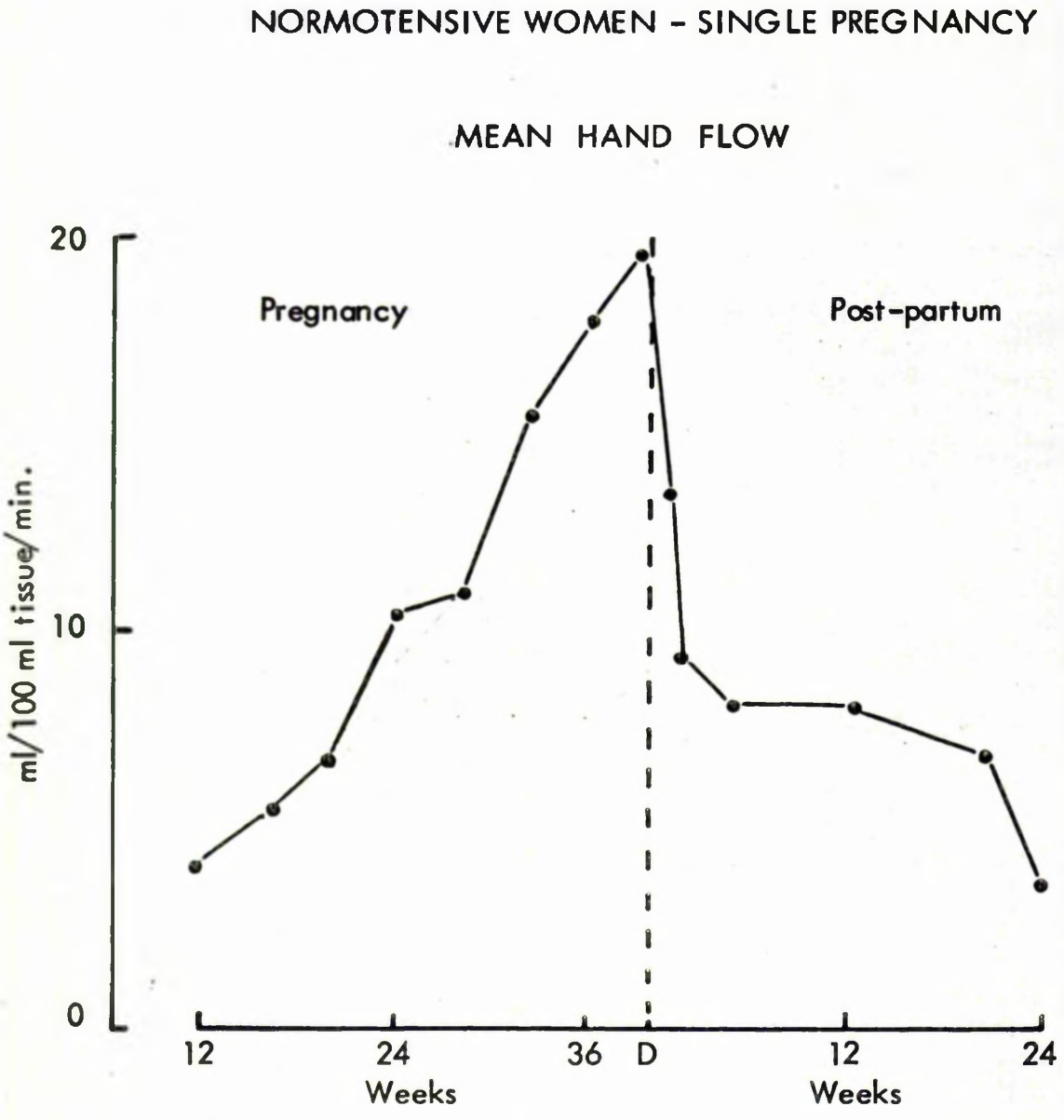


Fig. 6. Mean hand blood flow in normotensive women with a single pregnancy, measured during pregnancy and the puerperium.

The dotted line indicates delivery.

HAND BLOOD FLOW - TABLE I

Of the 52 healthy women, hand blood flow was measured in 32: 19 were primigravidae and 13 multigravidae. A total of 206 recordings were made in these women during pregnancy and the puerperium. The results in pregnancy were grouped into periods of four weeks and Table I gives the values obtained for each patient. Where more than one recording was made in a patient during the period indicated in the Table, only the average value is recorded and these occasions are indicated. The last column in pregnancy includes studies made from the 39th week until delivery; some deliveries were overdue. After delivery, the results on each day of the puerperium are given, since measurements were made on several days in some patients. Thereafter, a recording was made about six weeks after delivery. A few patients returned for studies during the subsequent weeks.

Fig. 6 shows the mean values for all the subjects. Mean hand blood flow rose uniformly from 4.1 ml/100 ml tissue/min before 14 weeks of pregnancy to 19.5 ml at term. Analysis of variance, as described earlier, showed that the regression of the slope of the duration of gestation - blood flow line was significant ($p < 0.001$) and that it did not deviate significantly from linearity ($p > 0.20$). The rate of increase was found to be about 0.6 ml/100 ml tissue/min per week. There was no evidence of a reduction in flow near or after term.

There was very little reduction in hand blood flow in the immediate puerperium. In patients in whom hand blood flow had been

TABLE I

HAND BLOOD FLOW - NORMOTENSIVE SINGLE PREGNANCY

ml blood/100 ml tissue/min.

	WEEKS OF PREGNANCY								DAYS AFTER DELIVERY								WEEKS AFTER DELIVERY			
No.	Under 14	15-18	19-22	23-26	27-30	31-34	35-38	39-D	1	2	3	4	5	6	7	8-14	2-8	9-16	17-24	24+
1	6.3		2.6																	
2			13.1	9.8	11.0*	7.5	11.3	16.3*	5.9				4.1							2.2
3								18.2*								9.1*	2.4			
4										15.4		10.8			8.4		9.7	5.6	7.6	
5							13.5*	14.1	17.1	6.9										
6	2.0	3.3	7.2		14.9	30.8	24.4*	27.5*	22.0	20.1		15.2	20.5				10.7			
8							14.0		10.0											
9	7.2			24.7			23.4		24.1						26.1		19.0			
10		12.9				14.3	29.0	16.7			2.7				8.5		4.1			
11	4.2	4.8		9.6	6.9	15.7	17.1	16.6	18.8				11.1				13.8			
12	3.0			9.1			18.8		18.3	19.1										
13			6.7	7.8		8.6	11.1	26.7	14.7								8.5	11.4		
16	1.4*	3.2	4.0	8.2	6.6	20.8	28.0	30.2					8.7							
17							10.4				17.5					9.4	9.2	13.1	9.7	
23					16.3			14.8						17.0				6.7		
24	1.8*	6.9		8.9			15.9*	17.4		17.1	9.9			12.8				3.8		5.0
25						16.2	22.5			9.2										
27					20.0			29.0		13.4					15.8		6.8			
28					2.1	7.4	7.1	15.6				20.9	7.4				1.6			
29	1.9			3.9		7.7	7.7										5.4	3.5	5.5	
30						17.5	8.6*								7.1				10.7	
31								15.9*					6.2				7.0			
32			12.1		14.7	21.9	14.0	18.1			12.8		13.4	7.6						
36									7.0	14.4		13.6			22.4		8.4	12.8	4.7	
38						14.5	9.8								5.4		6.9			
39				19.2			33.8							15.0			5.7			
40						16.8		15.5						15.3						
41									21.5	14.2	13.3			27.2	21.5		10.2	7.9	3.0	
43		1.4	1.2	2.9		9.0	12.2*				3.4				3.7					
45					6.5	20.9	16.2*	20.1*			13.9	8.9			10.4					
46						16.8	17.4													
50	8.7	5.9					44.6													
									15.9	14.4	10.5	15.1	10.0	15.8	12.9					
MEAN	4.1	5.5	6.7	10.4	11.0	15.4	17.9	19.5				13.4				9.3	8.1	8.1	6.9	3.6

* average of recordings made on more than one occasion.

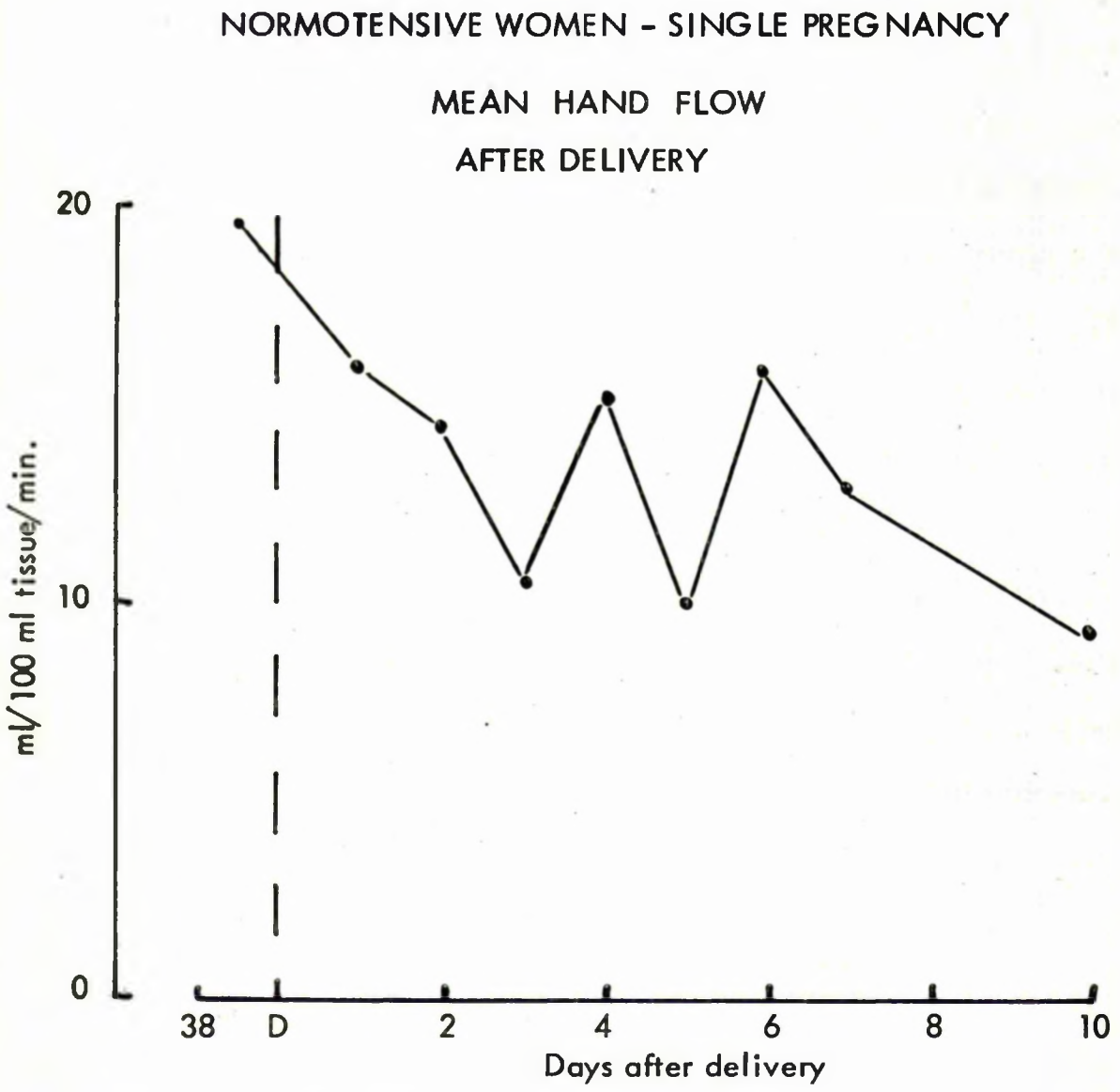


Fig. 7. Mean hand blood flow on each day of the first week of the puerperium in normotensive women with a single pregnancy. The value for the group between 38 weeks and delivery is given for comparison.

measured in late pregnancy (35 weeks onwards) and again in the first 48 hours after delivery, a Student's t-test to compare the mean values, showed that the reduction in hand blood flow after delivery was not significant ($t = 1.93$, $d.f. = 20$, $p > 0.05$). Fig. 7 shows the mean hand blood flow for each day during the first week after delivery. Although there appeared to be a reduction in hand blood flow during the first week following delivery, the variation in the values from different patients on any one day was too great for this reduction to be statistically significant. For instance, the mean value of 14.0 ml on the sixth and seventh days does not differ significantly from the mean of 15.2 ml on the first two days of the puerperium when tested by Student's t-test ($t = 0.689$, $d.f. = 33$, $p > 0.4$). Since most women who had an uncomplicated labour, delivery and puerperium went home about the seventh day, the number of recordings for the second week of the puerperium is few. By the sixth week, the mean hand blood flow had fallen to 8.1 ml. This value is significantly greater than the mean value (4.1 ml) obtained before the fourteenth week of pregnancy ($t = 2.54$, $p < 0.02$). The mean level of the subsequent period (to sixteen weeks after delivery) was still significantly greater than in early pregnancy ($t = 2.47$, $p < 0.05$). However, the number of subjects was fewer and many of the individual levels were so close to normal non-pregnant values that it is considered that normal levels were gradually attained about this time.

Effect of Parity

Sub-division of the group into primigravidae and multigravidae, as indicated in Table II, shows that there was a comparable increase in hand blood flow in both groups of pregnancy. Hence, the change in blood flow is not related to parity.

TABLE II - Mean Hand Blood Flow in Normotensive Pregnancy in Relation to Parity

ml blood/100 ml tissue/min.

STAGE OF PREGNANCY (WEEKS)	PRIMIGRAVIDAE	MULTIGRAVIDAE
Under 14	3.4 (4)	4.5 (5)
15 - 18	6.0 (4)	4.4 (3)
19 - 22	7.8 (5)	4.0 (2)
23 - 26	9.2 (3)	9.5 (6)
27 - 30	12.5 (8)	9.2 (2)
31 - 34	18.1 (10)	10.9 (6)
35 - 38	17.7 (13)	18.1 (10)
39-Delivery	19.8 (12)	18.6 (4)

Number of studies at each stage in parenthesis.

Effect of Lactation

Since the majority of patients were lactating successfully in the immediate puerperium and only a few had their lactation suppressed,

NORMOTENSIVE WOMEN - SINGLE PREGNANCY

MEAN FOOT FLOW

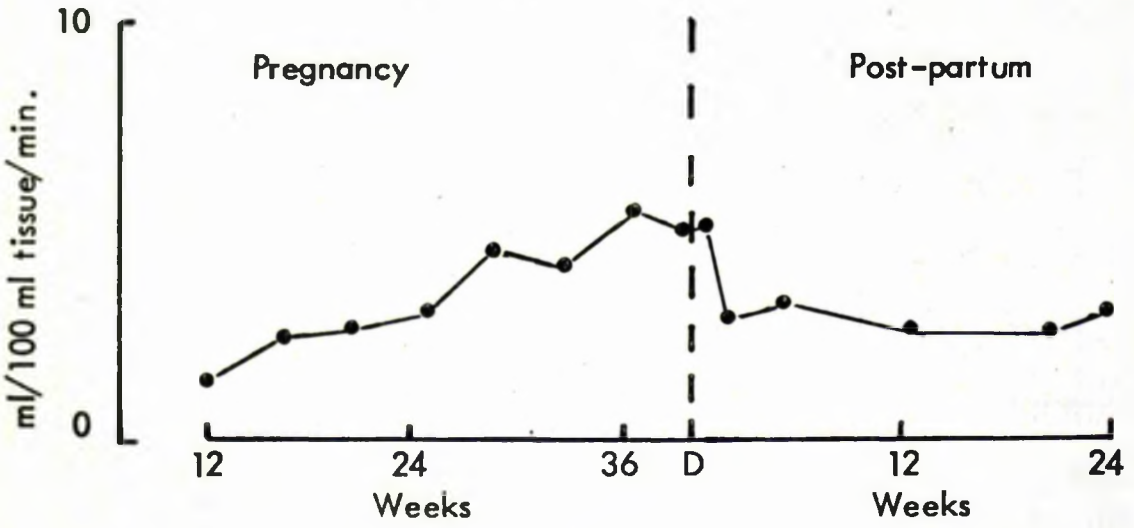


Fig. 8. Mean foot blood flow in normotensive women with a single pregnancy, measured during pregnancy and the puerperium.

The dotted line indicates delivery.

it was not possible to obtain comparable groups. However, there was no obvious reduction of hand flow in the patients who were not lactating. Mean hand flow during the first week of the puerperium was 13.8 ml in 49 studies in those lactating compared with 12.7 ml in 9 studies in those who were not. Six weeks after delivery, the mean hand blood flow in 7 lactating women was 7.5 ml compared with 8.5 ml in 9 women who were not.

FOOT BLOOD FLOW - TABLE III

Foot blood flow was studied in 28 of the group of 52 healthy women. There were 18 primigravidae and 10 multigravidae. A total of 161 estimations were made. The results, given in Table III, are again according to periods of four weeks in pregnancy, a single average for each patient being given when more than one study was made. Fig. 8 shows the mean values obtained for the group.

Mean foot blood flow increased from 1.5 ml before 14 weeks to 5.0 ml at term. Analysis of variance, carried out as in the hand blood flow, showed that the increase of flow related to weeks of gestation was significant ($p < 0.01$) and that the slope of the line did not deviate significantly from linearity ($p > 0.20$). The rate of increase was about 0.14 ml/100 ml tissue/min per week; considerably less than that found in the hand.

Foot blood flow remained elevated during the first week of the puerperium, analysis of variance showing that the regression of the slope of the gestation - blood flow line was not significant ($p > 0.20$).

TABLE III

FOOT BLOOD FLOW - NORMOTENSIVE SINGLE PREGNANCY

ml blood/100 ml tissue/min.

	WEEKS OF PREGNANCY								DAYS AFTER DELIVERY								WEEKS AFTER DELIVERY			
No.	Under 14	15-18	19-22	23-26	27-30	31-34	35-38	39-D	1	2	3	4	5	6	7	8-14	2-8	9-16	17-24	24+
1	1.3		1.5		3.7	5.2	2.8													
2				4.4	2.1		3.0													3.8
4							5.1	5.9	5.0	11.1		3.0			3.7		2.5	2.3	3.1	
6		2.0				4.1	9.1	4.2		6.5		3.4					2.0			
7				3.4	2.0			2.1						3.3			5.4			
9	1.2			4.0			7.6		8.5						5.5		9.4			
10	3.5*	8.0		5.1	4.7	2.7	7.6	3.0			2.5				3.0		2.5			
14						1.4		6.6			7.2									
15		1.8		2.3	6.1	3.0	1.6													
16	0.8	1.1	0.9	1.2	1.4	3.7	3.8	1.0						2.4						
17	2.2	1.1	1.5			5.9	1.6	7.5			5.1					4.2	4.5	4.8	3.6	
23					1.7		6.1	2.3								2.0		1.8		
25			4.4	3.6		3.9	6.1*	6.3		2.1										
27					8.1			6.2		3.1					4.9		2.3			
29	1.1			1.5		1.1	1.1										1.8	1.1	1.5	
30						3.3									1.5				2.8	
35	1.0	1.2			1.3			2.6									3.1			
36							3.4		3.8	3.5		2.9			8.8		2.5	4.3	2.7	
37			7.7		12.6												2.5			
38						1.6	5.1								5.6		3.6			
39				3.1		6.4	6.3	7.6									1.8			
40							3.1	6.7				11.7								
41									9.6	4.5	7.1			6.7	10.7		1.5	1.4	1.5	
42							2.9				1.1									2.3
44							18.2													
46						5.7	4.5													
47	1.0		0.8	1.9	4.2	3.2	9.2	7.6*						4.3		2.5	3.9			
50	1.2		2.7			12.4														
									6.7	5.1	4.6	5.3		4.2	5.5					
MEAN	1.5	2.5	2.8	3.1	4.4	4.2	5.4	5.0				5.2				2.9	3.3	2.6	2.5	3.0

* average of recordings made on more than one occasion.

The mean level of 3.3 ml six weeks after delivery was considered to be close to the non-pregnant level. As shown in Table IV, the increase in blood flow in primigravidae and multigravidae was similar. There was no difference in blood flow whether lactation occurred or not. During the first week of the puerperium, mean foot blood flow was 5.3 ml in 26 studies in women who were lactating compared with 4.6 ml in 5 who were not. Six weeks after delivery the mean value was 2.9 ml in 8 studies in lactating women compared with 3.8 ml in 7 studies in those who were not.

TABLE IV - Mean Foot Blood Flow in Normotensive Pregnancy in Relation to Parity

ml blood/100 ml tissue/min.

STAGE OF PREGNANCY (WEEKS)	PRIMIGRAVIDAE	MULTIGRAVIDAE
Under 14	1.6 (6)	1.2 (3)
15 - 18	2.5 (6)	-
19 - 22	2.5 (5)	3.6 (2)
23 - 26	3.0 (6)	3.1 (4)
27 - 30	4.9 (9)	1.9 (2)
31 - 34	3.7 (11)	5.8 (4)
35 - 38	4.7 (13)	6.7 (7)
39-Delivery	5.4 (11)	3.4 (3)

Number of studies at each stage in parenthesis.

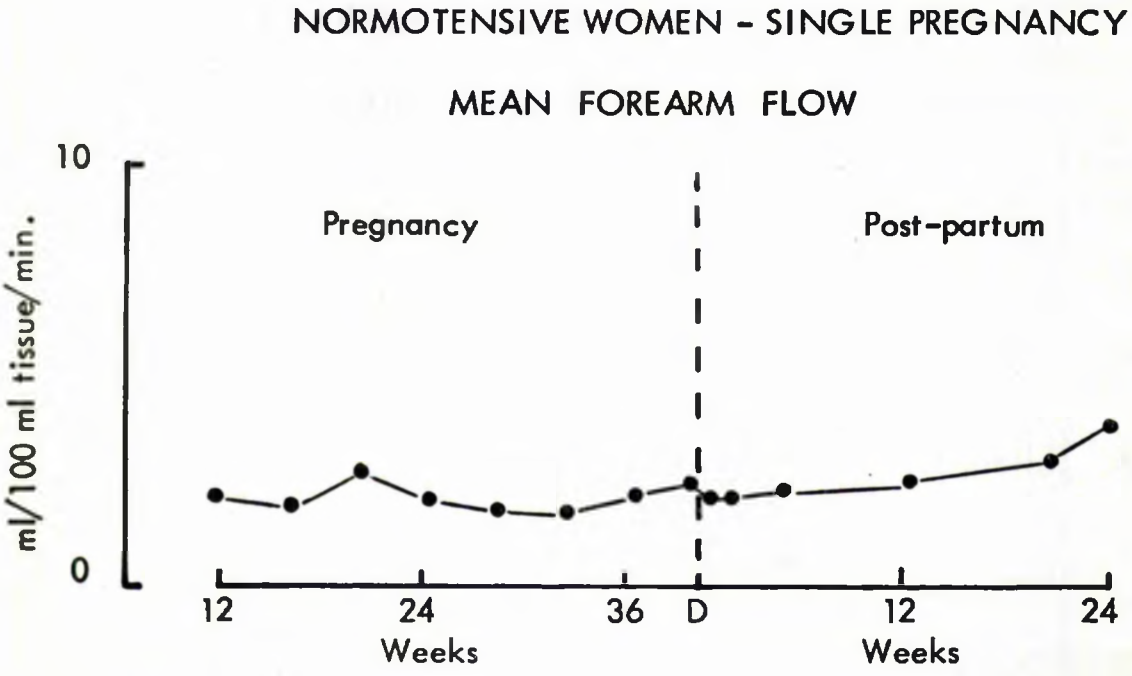


Fig. 9. Mean forearm blood flow in normotensive women with a single pregnancy, measured during pregnancy and the puerperium.

The dotted line indicates delivery.

FOREARM BLOOD FLOW - TABLE V

Forearm blood flow was studied on 177 occasions in 30 of the group of healthy women. There were 20 primigravidae and 10 multigravidae. Table V shows the results according to subject and stage of gestation. There was no tendency for the forearm blood flow to increase as pregnancy progressed, the mean level at term being 2.4 ml compared with 2.1 ml in early pregnancy. Fig. 9 shows the mean values for the group throughout pregnancy and the puerperium. As expected, from the mean values, analysis of variance showed there to be no significant increase of blood flow with time during pregnancy and the puerperium. The effect of parity and lactation have not been considered separately.

CALF BLOOD FLOW - TABLE VI

Calf blood flow recordings were made on 89 occasions in 15 of the healthy women. There were 10 primigravidae and 5 multigravidae. Table VI shows the values obtained in the individual subjects and Fig. 10 illustrates the mean values for the group. There was little variation in the mean values obtained during pregnancy and the puerperium. As in the forearm, analysis of variance showed no increase.

PULSE RATE

The pulse beat is recorded on the plethysmographic record (see Fig. 5, opposite p. 39). During a limb flow recording, at a time when the patient was relaxed and comfortable, 50 pulse beats were timed and the pulse rate calculated. No blood flow recordings were taken during

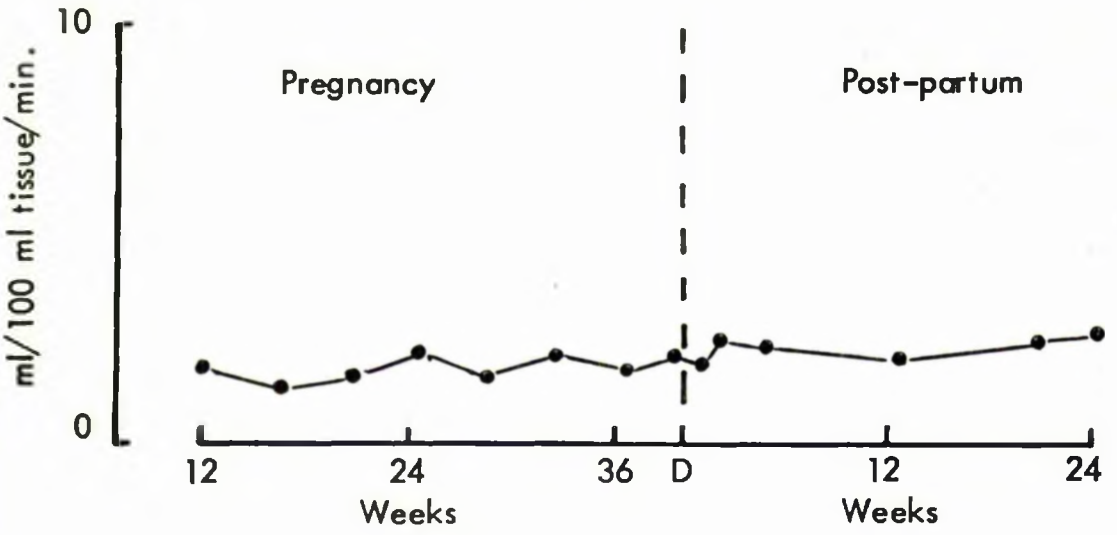


Fig. 10. Mean calf blood flow in normotensive women with a single pregnancy, measured during pregnancy and the puerperium.

The dotted line indicates delivery.

TABLE V

FOREARM BLOOD FLOW - NORMOTENSIVE SINGLE PREGNANCY

ml blood/100 ml tissue/min.

No.	WEEKS OF PREGNANCY								DAYS AFTER DELIVERY								WEEKS AFTER DELIVERY			
	Under 14	15-18	19-22	23-26	27-30	31-34	35-38	39-D	1	2	3	4	5	6	7	8-14	2-8	9-16	17-24	24+
2				2.5	2.3		3.2													4.4
3								2.9*									0.8			
5							1.9	2.7	0.9	3.7										
6	2.0	1.7	1.1		1.5	1.3	1.8	2.4*					1.9							
8							1.7		1.9							2.8				
11	1.7			3.6	1.3	1.5	2.3		3.1				2.5				1.8			
13			3.9	2.2		1.5*	2.3										3.3			
18	2.5	2.7	2.8	2.6	2.8	2.1	1.7		2.3							1.8	1.6			
19			1.9	1.9																
21							1.9	1.6				1.6			1.8		1.7			
22							2.9	2.1			3.8						4.1			
23					2.0	1.9	1.9		2.9							1.6		2.6		
24	2.6*	1.6		1.3			2.3	2.0		0.4	1.4									3.5
26		1.5		1.6	1.5	1.5														
28												1.7	2.6					2.5		
30						2.5	1.8								2.9				3.1	
31								4.5*					3.0				2.0			
32			3.2		2.6	1.9		3.0			1.5		1.6	0.7	0.7					
33			2.4	1.5																
34		2.6	2.1	1.4	1.8	1.7		1.8									1.6			
37			3.1	3.1	1.0	2.1	2.4	1.6									2.0			
40							3.5	2.6	1.7					2.7			3.8			
41	2.1		2.1			1.3		2.0		1.8							1.8			
43		1.2	1.6	1.2		1.7	1.2				1.3									
45					1.4		2.0	2.3			3.7		3.3		2.3					
48	2.4		4.0	3.2	3.3	2.4	2.5	2.2	2.5								3.2			
49						2.1	1.9	2.8		1.4							2.3			
50	1.6	2.3		2.0	1.5	1.3	1.8	1.7					1.3							
51							1.8	2.1			2.4									
52				1.7	2.0	2.5	2.8				1.9						1.9			
									2.2	1.8	2.3	1.6	2.3	1.7	2.3					
MEAN	2.1	2.0	2.8	2.1	1.9	1.8	2.2	2.4				2.1				2.1	2.3	2.5	3.1	3.9

* average of recordings made on more than one occasion.

TABLE VI

CALF BLOOD FLOW - NORMOTENSIVE SINGLE PREGNANCY

ml blood/100 ml tissue/min.

	WEEKS OF PREGNANCY								DAYS AFTER DELIVERY								WEEKS AFTER DELIVERY			
No.	Under 14	15-18	19-22	23-26	27-30	31-34	35-38	39-D	1	2	3	4	5	6	7	8-14	2-8	9-16	17-24	24+
2			1.6	2.5	1.9	2.2	1.9						1.4							
3								2.8								3.3	1.7			
5							2.9	1.6	2.2	1.3										
6	1.6	1.2	1.2		1.2	1.5*	1.7*	2.0*									1.7			
11	2.4	1.3		2.3	1.3		2.3	2.1									3.5			
13			1.5	2.0	2.3	2.3	1.6										2.1			2.6
23								1.1						2.0				2.1		
25	1.3*			1.5			1.2*	1.2				1.6								1.7
28					1.0	1.8	1.7	1.9					1.7			1.7				
30						2.2	2.0								1.0				2.5	
31								3.2					3.0				2.3			
32			2.1		1.1	2.1		3.0					1.1	0.9						
40						3.6	1.3					4.2								
43		1.4	1.7	2.3		1.9	1.9*				1.5									
45					1.3	1.2	1.6*	2.1*			3.7		2.2		1.7					
									2.2	1.3	2.1	2.8	1.9	1.5	1.3					
MEAN	1.8	1.3	1.6	2.1	1.6	2.1	1.8	2.1				1.9				2.5	2.3	2.1	2.5	2.7

* average of recordings made on more than one occasion.

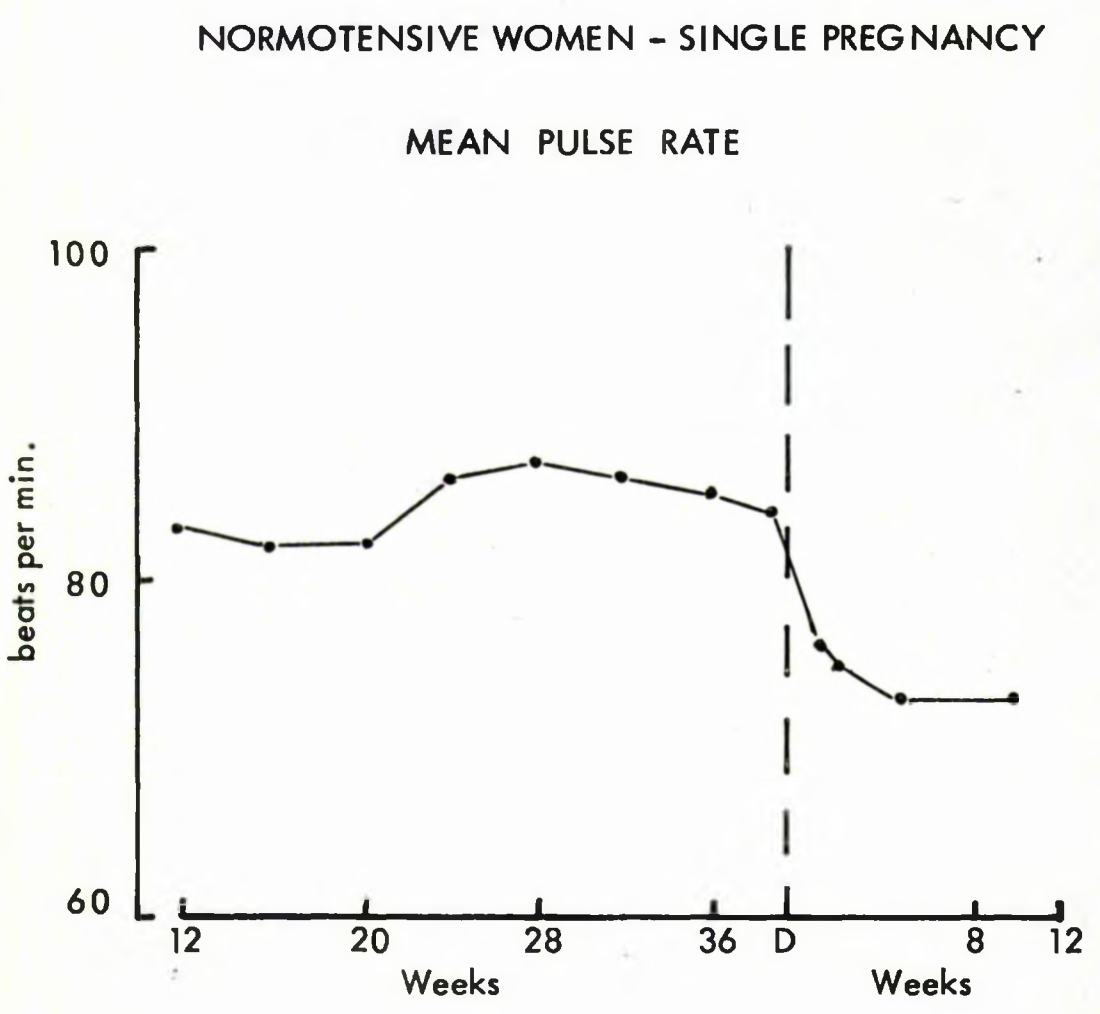


Fig. 11. Mean pulse rate in normotensive women during pregnancy and the puerperium.

this time and the patient was unaware that her pulse was being counted. An average pulse rate was thus obtained for each occasion of limb flow recording. The number was less than the total of 633 limb flow recordings since more than one segment was usually measured at a single session. The pulse rates obtained in the group of 52 healthy normotensive women were sub-divided into the same stages of pregnancy as the limb flow measurements and the mean values are shown in Fig. 11. A table with these mean values and the range of values for the group is given later (Table XXII, p.105) with the corresponding values in twin and hypertensive pregnancy. Individual values are not tabulated for each of the 52 subjects, but to illustrate the variation between subjects, Table VII shows serial readings in 12 of them throughout pregnancy and the puerperium. In normotensive single pregnancy, considering the range obtained, the mean pulse rate throughout pregnancy is essentially constant and is maintained at about 10 - 15 beats faster than the values obtained at least six weeks after delivery. These findings are in accordance with the conclusion reached by Hytten and Leitch (1964) (see p. 11).

ARTERIAL BLOOD PRESSURE

The average blood pressure reading during each experimental session for each patient was recorded. The values were tabulated according to gestation, using the same time intervals as were used to sub-divide the limb blood flow results. When measurements had been made on more than one occasion within any interval a single average

TABLE VII PULSE RATE - NORMOTENSIVE SINGLE PREGNANCY

SUBJECT NO.	WEEKS OF PREGNANCY								WEEKS AFTER DELIVERY	
	Under 14	15-18	19-22	23-26	27-30	31-34	35-38	39-D	D-1	6+
6	70	65	85	-	73	67	67*	65*	64*	58
10	78*	94	-	100	92	88	100	91	78*	83
11	-	76*	-	92	76	84	100	80	87*	64
18	92	88	92	94	82	88	105	-	88	78*
24	81*	-	85	76	-	-	97*	85	79*	-
29	-	-	-	72	-	86	84	-	-	58*
34	-	91	88	92	94	97	-	86	-	82
37	-	-	88	89	96	92	78*	-	-	67
41	80	-	77	-	-	85	-	77	67*	63*
47	92	-	96	-	96	107	107	98*	68	79
48	85	88	88	-	90	85	87	80	73	84
50	75	81	-	68	72	82	87*	-	59	-

* Average of more than one occasion.

NORMOTENSIVE WOMEN - SINGLE PREGNANCY

MEAN BLOOD PRESSURE

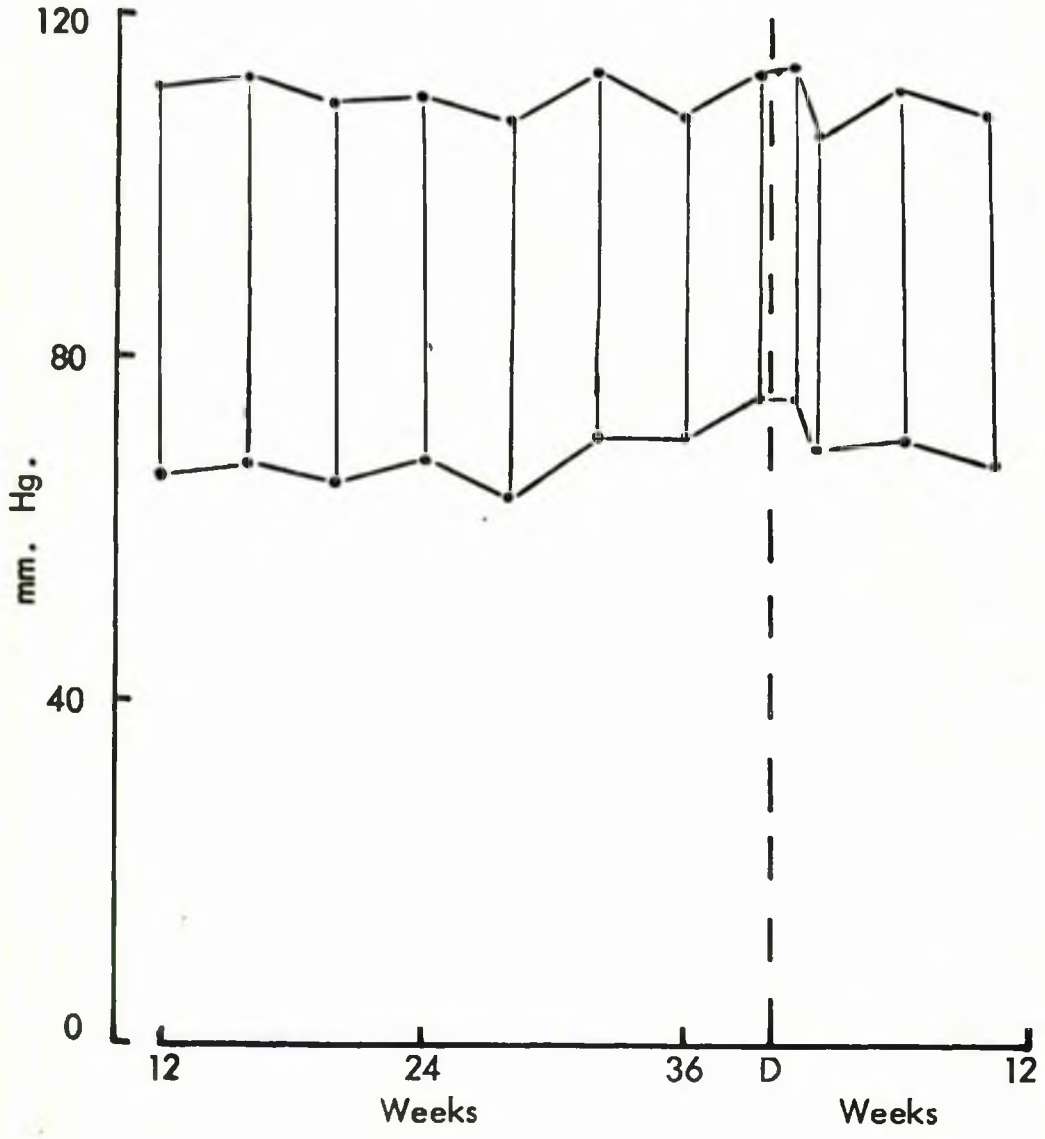


Fig. 12. Mean arterial systolic and diastolic blood pressure during pregnancy and the first 12 weeks after delivery, in the group of normotensive women.

was taken for each subject. The average systolic and diastolic pressures for each stage were then obtained (Fig. 12). Systolic blood pressure was constant in the group studied. There was an increase in diastolic blood pressure in late pregnancy, the value near term being 75 mm Hg compared with 65 mm Hg in the first trimester. This accords with previous studies (see p. 9).

SUMMARY OF OBSERVATIONS OF LIMB BLOOD FLOW IN HEALTHY, NORMOTENSIVE WOMEN IN PREGNANCY

A progressive increase in hand blood flow occurs during normal pregnancy. This increase is sustained in the immediate puerperium and the flow returns to normal levels over several weeks.

There is a similar progressive, though smaller, increase in foot blood flow which is also sustained in the early puerperium. Normal levels are, however, reached by six weeks after delivery.

There is no change in forearm and calf blood flow during pregnancy and the puerperium.

An approximate estimate of the increased blood flow to the extremities in late pregnancy can be made. Assuming the average volume of each hand to be 400 ml, an increase of 15 ml/100 ml/min represents an increased blood flow of 60 ml in each hand. Similarly, an average blood flow of 3 ml/100 ml/min to each foot, of approximately 1000 ml represents an increased flow of about 30 ml to each foot. An additional flow of approximately 150 ml per minute is therefore passing through the limbs in late pregnancy.

DISCUSSION

COMPARISON OF RESULTS WITH PREVIOUS STUDIES

These results show that vasodilatation in the limbs in normal pregnancy is apparently confined to the distal parts of the extremities, namely the hands and feet. The findings are in general agreement with the results of Abramson and his colleagues (1943) but do not support the reports of an increased flow, claimed by later workers (Burt 1950, Herbert et al. 1958, Spetz 1964) to the forearm or calf. The quantitative findings necessarily depend on the method of study and the exact experimental conditions but several of the variations from previous work are worthy of discussion.

The five-fold increase in hand blood flow found in this study is large compared with Mendlowitz's findings (1958) for digital blood flow (0.29 $cm^3/cm^2/min$ in the third trimester of pregnancy compared with 0.20 in non-pregnant control women). In the comfortably warm non-pregnant subject when hand blood flow is high, a greater proportion of the total hand flow passes through the digits (69%) than when hand blood flow is lower, in a cooler environment (43.8%) - (Greenfield, Shepherd and Whelan 1951). This variation is considered to be due to the opening of arterio-venous anastomoses in the finger tips to facilitate heat loss. We would therefore expect that in pregnancy where the hand blood flow is greatly increased the digits would share the increase to at least a commensurate extent. However, the methods used are not directly comparable and a differential method of studying hand flow

would be required to establish this point.

The more recent report from Sweden by Spetz (1964) showing a progressive increase in mean forearm blood flow from 2.1 ml/100 ml/min in early pregnancy to 12.3 ml near term is widely at variance with the findings in the present study. Spetz' results are based on serial recordings under standardised conditions with full statistical analysis, although the magnitude of change renders this somewhat superfluous. Spetz concludes from his data that a six-fold increase in forearm blood flow is unlikely to occur in skin alone and considers that at least some of this increase occurs in blood flow to muscle. Since skeletal muscle constitutes about 40% of body weight (Spector 1956) the implication of his finding in terms of the cardiac output of the pregnant woman must be considered.

In studies on blood flow in non-pregnant subjects during fainting (Barcroft and Edholm 1945) a doubling of forearm blood flow was observed. The increased blood flow occurred in muscle only. The authors considered that the circulation in the forearm muscles is a reliable index of changes elsewhere in skeletal muscle and estimated that a comparable dilatation in other skeletal muscle would increase the total muscle blood flow from 800 to 2000 ml/min. If even one part of the six-fold increase in forearm blood flow, found by Spetz, occurred in muscle, this would involve approximately a litre of blood per minute. Any quantitative estimate thus derived is necessarily approximate but clearly any substantial increase in muscle blood flow represents an

enormous and, in pregnancy inexplicable, diversion of cardiac output. Therefore, the discrepancy with the present results merits careful consideration of possible differences.

Spetz' results refer to ten women representative of the twenty-seven studied. Despite considerable variation in the actual levels of forearm flow, there is a substantial increase in late pregnancy in every subject. There are, however, several important differences in technique which make comparison with the present series difficult:-

1) Room Temperature. A temperature of 22°C was maintained compared with 20°C in the present study. This increase in environmental temperature could be associated with a relative increase in skin blood flow.

2) Water Temperature. A temperature of 36°C was used for the surrounding water jacket compared with 34°C in the present study.

That temperature of the water-bath has a profound effect on forearm blood flow was shown by Barcroft and Edholm (1943). In the same subjects under otherwise standardised conditions, the mean forearm blood flow after 30 - 60 minutes in water at 30°C was less than 2 ml/100 ml tissue/min compared with 12 ml at 40°C. At intermediate temperatures the differences are less but there is a slight fall over one hour at 32°C and a slight rise at 35°C. On the basis of these experiments, a forearm water-bath temperature of 34°C has been the usual one employed subsequently in physiological observations.

3) Duration of Observations. After assembly of the apparatus 30 minutes elapsed before any measurements were made.

In the present study, preparation of the equipment, recording of the blood pressure and assembly of the apparatus occupied 20 to 30 minutes and after any necessary adjustments had been made, recordings were commenced. A further wait of 30 minutes before starting is readily tolerated by most subjects, but women in late pregnancy in the supine position are liable to become uncomfortable and anxious if they cannot move freely. Furthermore, if the total time for the procedure is long, they often wish to micturate before readings are completed. Emotional factors have been shown to increase muscle blood flow (Abramson and Ferris 1940, Blair, Glover, Greenfield and Roddie 1959). On a few occasions in the immediate puerperium in the present series, anxiety about whether the baby, who was out of earshot, was requiring attention was found to cause lability of flow recordings. This anxiety was not indicated by the patient at the time but was obvious from an increase in forearm blood flow and the patient's subsequent remarks.

While such factors are unlikely to have occurred in all of Spetz' patients, prolongation of the total time for the procedure could have caused raised levels of forearm flow in some women in late pregnancy.

4) Simultaneous Arterial and Venous Cuff Occlusion. When supra-systolic pressure is applied to the wrist some blood is displaced into the forearm, the increase in volume subsiding after 15 seconds. When

Kerslake (1949) investigated the effect of the application of this wrist arterial cuff on forearm flow measurement, he found that, starting five seconds after occlusion the readings were initially higher (by about 25%) then lower than those recorded after one minute when a stable level was reached. The effect is a local one, presumed to result from the alteration in haemodynamics of the arterial system in the forearm and could represent either a real or an apparent increase in forearm flow. It is probable that simultaneous cuff application as used by Spets would include at least this magnitude of error. At the moment of simultaneous occlusion the blood intended for the hand is already contained within the large forearm arteries. Being prevented from reaching the hand it must be captured by the venous occlusion. Since, as shown in the present study, hand blood flow is greatly and progressively increased in pregnancy, an apparent increase in forearm flow in late compared with early pregnancy might well occur. Spets (1964) allowed at least one minute between recordings and there would be time therefore for the hand flow to be restored between every recording. This seems to be a very serious objection to the method employed by Spets.

In order to test the validity of these deductions, forearm flow was measured under varying conditions of temperature and cuff application in 4 healthy women in pregnancy and the puerperium and in one non-pregnant subject.

Table VIII a) refers to 8 measurements on the 4 pregnant women when only water-bath temperature was altered. One was studied twice and in 3 the procedure was repeated after delivery. After "control" forearm flows had been taken as carried out in the present series, the water temperature was increased to 36°C and maintained for 30 minutes. A further series of recordings was then made. On each occasion, there was an increase in flow but there was considerable variation in the amount. The average level rose from 2 ml/100 ml/min to 3.41 ml - an average increase of 76.2%.

The procedure was repeated on a different occasion in the four subjects and also in the non-pregnant subject when the room temperature was also increased to 22°C over the 30 minute period. The mean forearm flow increased from 2.62 ml/100 ml/min to 4.08 ml, an average increase of 55.5% which is no greater than that obtained by local heating only (Table VIII b).

It is therefore concluded that increasing the room temperature to 22°C and the water-bath temperature to 36°C increases forearm blood flow by at least 50%. Since the experimental conditions were altered to assess the role of these relatively minor temperature variations in accounting for the difference between Spets' results and the present series, no firm conclusions can be drawn concerning a difference in response to indirect heating in pregnancy compared with after delivery. However, these results suggest no consistent difference with the exception of one patient studied at 37 weeks of pregnancy when the

TABLE VIII

a) Plethysmograph Water Bath Temperature Raised to 36°C - Effect on Forearm Blood Flow.

STAGE OF PREGNANCY WEEKS	FOREARM "CONTROL" FLOW ml/100 ml tissue/min	FOREARM FLOW AFTER 30 mins at 36°C. ml/100 ml tissue/min	% CHANGE
21	2.4	4.8	+ 100
29	1.3	2.3	+ 77
37	1.7	5.8	+ 241
40	2.2	3.3	+ 50
40	1.9	2.7	+ 42
D + 1	1.8	3.3	+ 83
D + 1	2.5	2.6	+ 4
D + 6	2.2	2.5	+ 13
MEAN	2.0	3.41	+ 76.2

b) Room Heating to 22°C as well as Water Bath Temperature Increase to 36°C - Effect on Forearm Blood Flow.

STAGE OF PREGNANCY WEEKS	"CONTROL" FLOW ml/100 ml tissue/min	AFTER HEATING ml/100 ml tissue/min	% CHANGE
31	1.7	2.5	+ 47
38	3.9	5.9	+ 51
D + 1	2.3	3.6	+ 56
D + 15	2.6	3.9	+ 50
Non-pregnant	2.6	4.5	+ 73
MEAN	2.62	4.08	+ 55.5

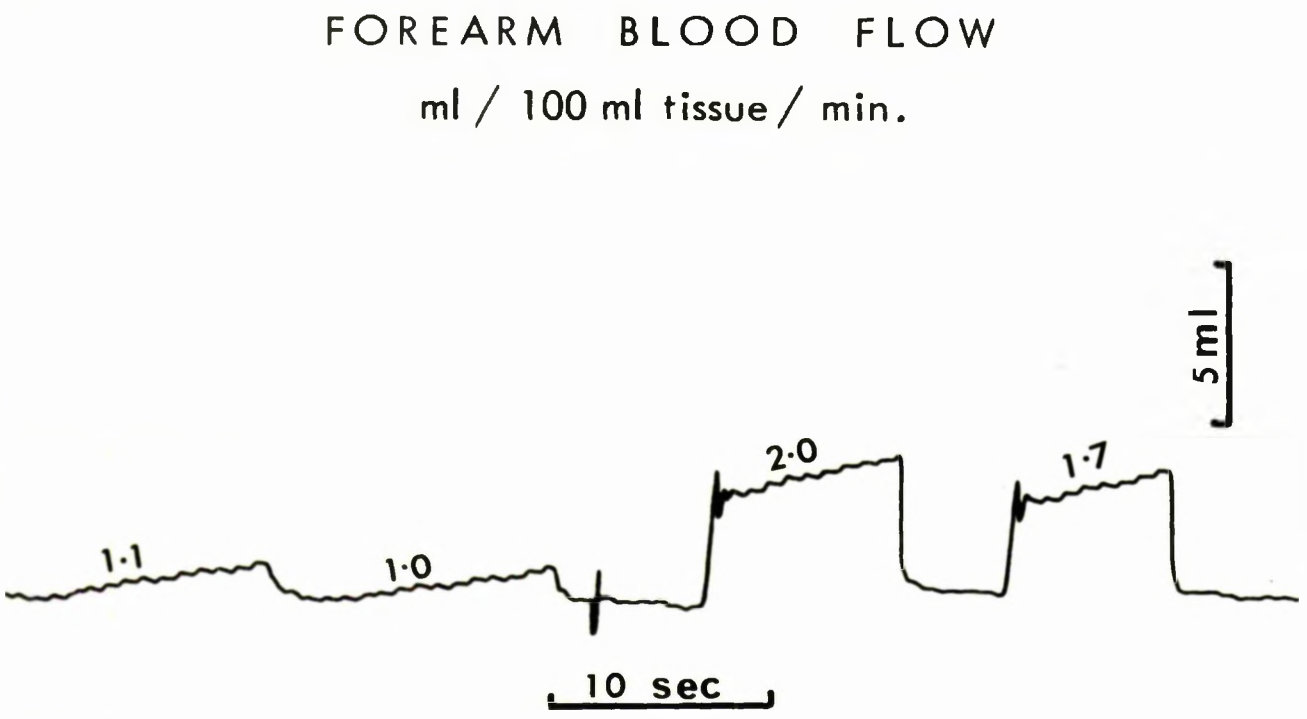


Fig. 13. Segment of forearm blood flow showing 2 recordings taken in the conventional manner followed by 2 recordings taken with simultaneous application of both arterial and venous cuffs.

percentage increase was 241% over the "control" level. The same subject showed an increase of + 51% when studied on another occasion in late pregnancy (referred to in Table VIII b) and + 83% in the puerperium. The isolated marked increase, out of proportion to the others in the series, may well be an example of the greater intolerance of a few subjects in late pregnancy to the more prolonged procedure involving relative immobility and possibly emotional factors.

The effect of simultaneous cuff occlusion was more difficult to assess. Fig. 13 shows two flow recordings under standard conditions followed by two where simultaneous occlusion of both cuffs was made. The recordings refer to measurements made in the same subject in the course of the same session. When both cuffs are applied together there is a large immediate increase in volume or "artefact". This is greater than that normally obtained at distal occlusion and presumably represents the kinetic energy of the intended hand blood flow as well as additional blood. This disturbance makes interpretation of the initial part of the curve difficult. Reduction of this difficulty is obtained by increasing the distance of the distal cuff from the plethysmograph but this procedure entails the inclusion of venous return from a segment not under measurement. Where recordings were taken at 15 second intervals as illustrated in the record, it was consistently found that the first recording was higher than subsequent ones. Due to different possible interpretations of these distorted records, it was found difficult to make any quantitative comparison

of the effect of this technical variation but simultaneous cuff occlusion where the flow rate was already elevated due to local heating to 36°C frequently gave forearm flow rates of about 6 or 7 ml/100 ml/min.

Thus, even combining these variables did not give flow rates of the magnitude found by Spets. There may be other important variations in technique. All the differences discussed tend to increase forearm flow compared with the present series and some factors would apply to late pregnancy only, thus at least partly explaining the discrepancy in results.

POSSIBLE AETIOLOGY OF CHANGES OBSERVED IN THE PRESENT STUDY

Since only the distal segments of the limbs show an increase in blood flow in pregnancy, it is extremely unlikely that a circulating humoral vasodilator substance is responsible. A direct effect of oestrogen or progesterone is also unlikely since the increase in peripheral flow is sustained in the early puerperium while the blood (Roy, Harkness and Kerr 1963) and urinary (Brown 1963) levels of oestrogens and the blood (Lurie, Reid and Villee 1966) and urinary (Kupperman and Epstein 1958) levels of progesterone fall sharply after delivery. Similarly, changes in adreno-cortical activity cannot be responsible since hand flow was increased, as in normal pregnancy, in a pregnant woman maintained on cortisone after bilateral adrenalectomy (see results in Table XIV, p. 86).

Comparison of the extent of increase in hand blood flow in pregnancy with the local effect of a vasodilator drug was possible in one patient (No. 24) who had been given chlorpromazine intra-arterially some years previously for experimental purposes. Hand blood flow had been measured at that time by the same method used in the present study. Chlorpromazine is a well recognised vasodilator substance (Foster, O'Mullane, Gaskell and Churchill-Davidson 1954, Ginsburg and Duff 1956). Infusion of 200 µg per minute of chlorpromazine for six minutes resulted in an increase of hand blood flow from 2.7 ml/100 ml/min to 8.0 ml/100 ml/min. In pregnancy, hand blood flow increased to a much greater extent; from 1.8 ml at 8 weeks to 17.4 ml

at 39 weeks of pregnancy (Table I).

Studies in recent years on the control of the circulation to the limbs have made it clear that the control of the blood flow to the hands is by vaso-constrictor nerves to the skin vessels controlled by the sympathetic nervous system (Barcroft 1960, Fox and Edholm 1963). The blood flow to the foot is also controlled by vasoconstrictor sympathetic nerves although Pickering and Hess (1933) showed that there is an unequal distribution of vasomotor tone in the hands and feet since vasodilatation on body warming occurred more readily and consistently in the hands than in the feet. Similarly, Allwood and Burry (1954) studying the effect of direct heating and cooling on the foot, showed that, as temperature increased the increase in foot blood flow was considerably less than the corresponding increase in hand flow. This is not due to a smaller percentage of skin or to a difference in vascularity and it was considered that vasoconstrictor release occurred less readily in the foot than in the hand.

By contrast, vasoconstrictor nerve activity has only a minor role in the control of the blood flow to the skin of the forearm, the main mechanism being vasodilator, secondary to sweat gland activity (Roddie, Shephard and Whelan 1957, Fox and Hilton 1958, Fox and Edholm 1963). Blair, Glover and Roddie (1960) have shown that the calf, thigh and upper arm behave similarly.

The blood vessels to the muscles of the limbs have both a sympathetic vasodilator and vasoconstrictor supply. Changes in blood

supply to skeletal muscle occur independently of changes in skin and do not occur in response to indirect temperature changes (Roddie, Shepherd and Whelan 1957). These authors have also shown that on body heating, vasodilatation in the hand and slight vasodilatation in the forearm occur due to release of sympathetic vasoconstrictor tone to the skin vessels, though the increase in forearm blood flow is seen only if the subject is cool to start with. Thereafter, as heating proceeds, a marked increase in forearm blood flow, accompanied by sweating, occurs.

Thus, changes in the blood supply of the hand and foot reflect, essentially, changes in blood supply to the skin mediated through sympathetic vasoconstrictor nerves. The forearm and calf may reflect changes in blood supply to either skin or muscle, the former being induced mainly by a cholinergic vasodilator mechanism while alterations in muscle blood flow may be constrictor or dilator sympathetic effects, responsive to different stimuli from those affecting hand blood flow.

The present results strongly suggest that there is release of sympathetic vasoconstrictor tone sufficient to cause vasodilatation in the hand and to a lesser extent in the foot. Further studies were made to determine if release of vasoconstrictor tone was complete and hand vasodilatation maximal.

In a healthy woman, 36 weeks pregnant, blood flow in both hands was measured simultaneously. The sympathetic nerve supply was then blocked on the left side. A solution of 0.3 ml of 1 in 1000 adrenaline

EFFECT OF NERVE BLOCK ON HAND BLOOD FLOW

IN LATE PREGNANCY

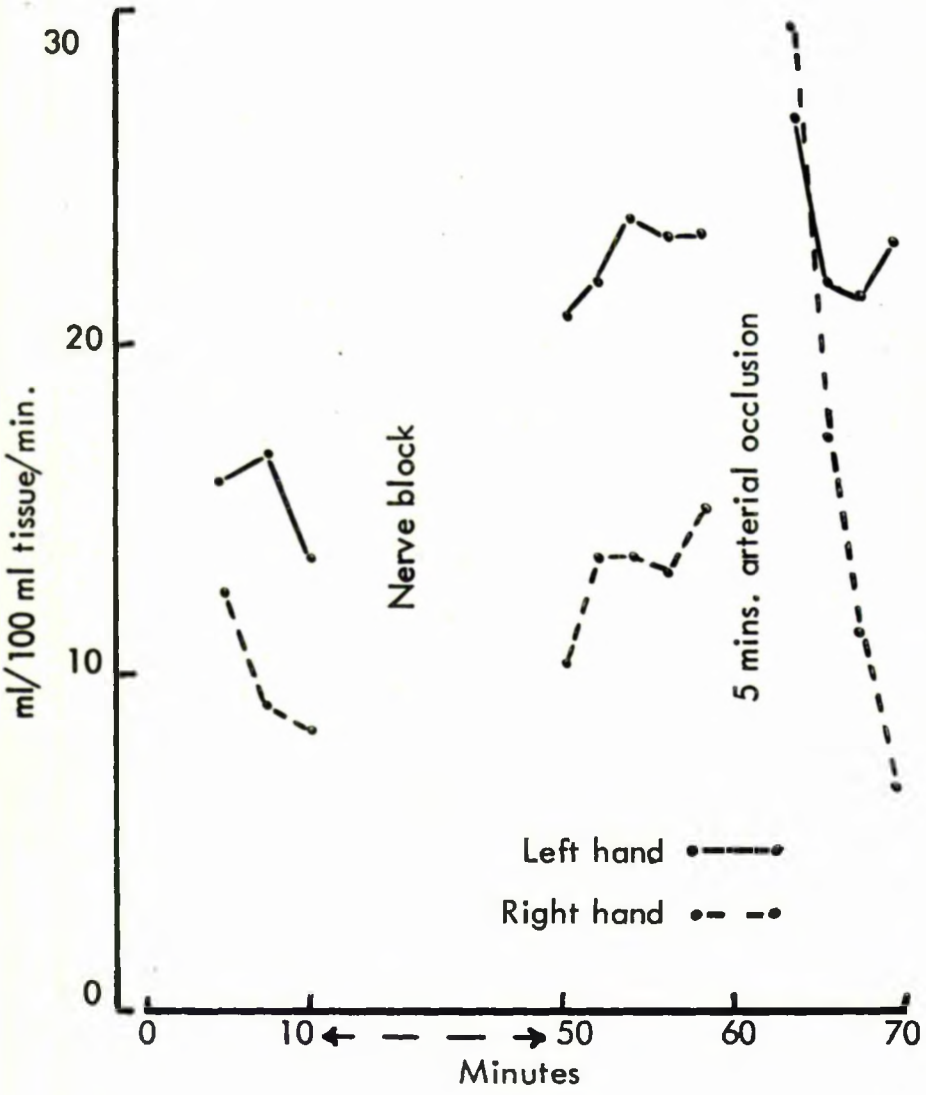


Fig. 14. Hand blood flow measured in both hands before and after nerve block of the left hand. The flow was higher on the left side after the block. After five minutes of arterial occlusion the flow was higher in both hands, returning to the control level rapidly on the unblocked side (right) and remaining high on the blocked side (left).

and 20 ml of 2% lignocaine was prepared: 5 ml were injected in the radial groove in the upper arm, 2 ml just above the medial epicondyle to block the ulnar nerve and 5 ml were injected just above the bifurcation of the brachial artery to block the median nerve. Sensation in the hand was not completely abolished but was greatly diminished. Thirty minutes after completion of the nerve block, further recordings were made. Fig. 14 shows the average blood flow per minute in each hand before and after the nerve block. In the left hand, flow rose from 15.2 ml/100 ml/min to 22.4 ml, an increase of 47.4%. However, in the right hand, the flow also increased by 30%. This increase in flow in the control hand was possibly due to relief of initial apprehension. If a comparable increase had occurred on the left side a flow of 19.9 ml would have been obtained. The actual increase in flow attributable to the block above the expected level is therefore only 12.4%. Arterial occlusion, a stimulus causing temporary vasodilatation independent of sympathetic activity resulted in a flow of 29.4 ml in the right hand during the first minute after release of occlusion and 26.6 ml in the left hand, showing that marked vasodilatation was already present on the left side but not on the right. These results show that in this patient, in late pregnancy, further hand dilatation could be obtained by nerve block and that sympathetic vasoconstrictor tone was not therefore completely released.

In another patient, 39 weeks pregnant, the effect of indirect heating was investigated. Resting flow in both hands was measured at a room temperature of 20°C, using water at 32°C in the plethysmograph.

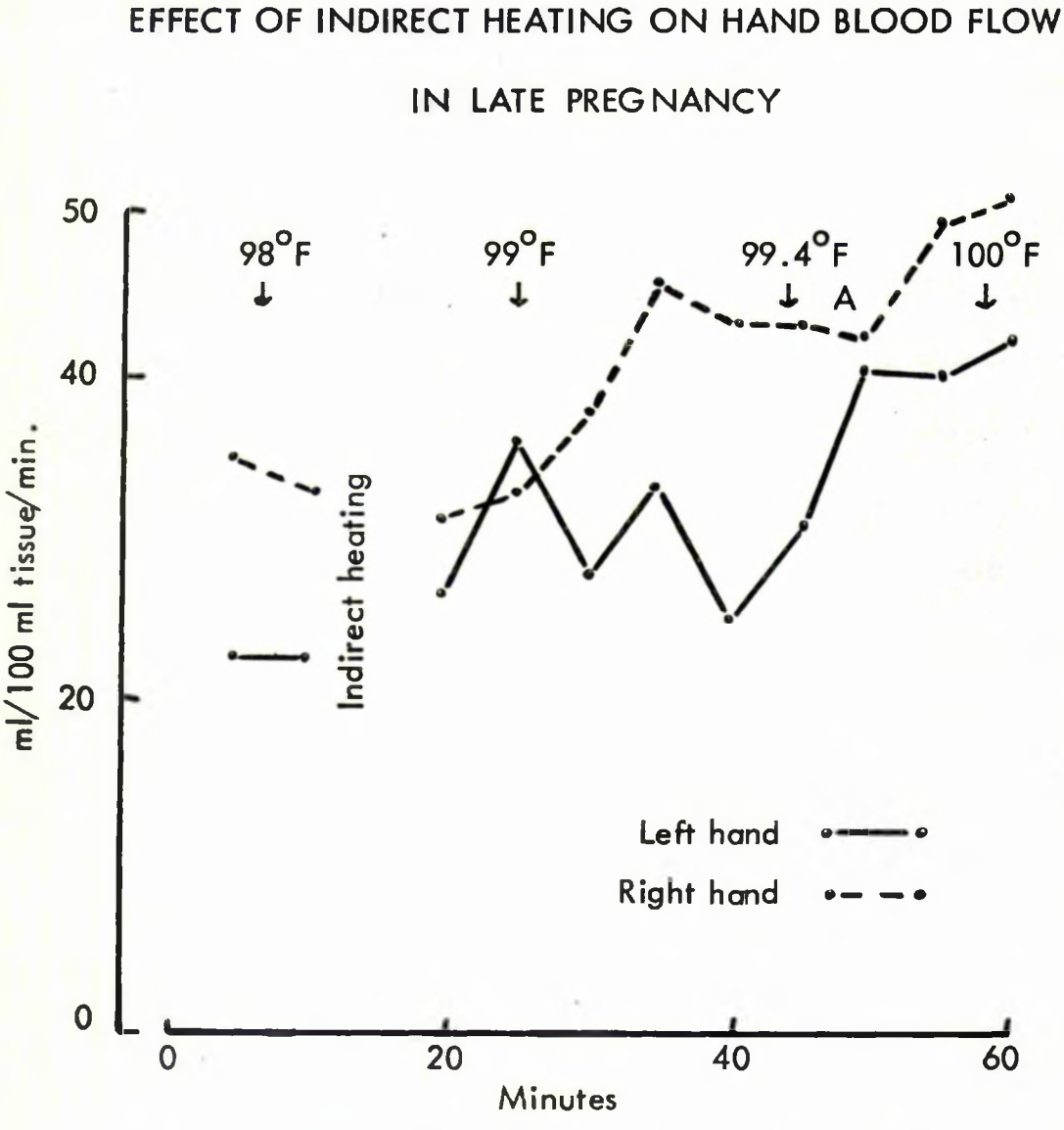


Fig. 15. Hand blood flow measured in both hands before and during indirect heating, as described in the text. Hand flow, initially higher in the right hand increased in both as heating progressed. At A, direct heating evoked a further increase. The increase in oral temperature is shown.

The patient's feet were then immersed in baths of stirred water at 43°C, a procedure known to release vasoconstrictor tone (Gibbon and Landis 1932). Ten minutes after the start of indirect heating recordings of hand flow were resumed at minute intervals and continued for a further 40 minutes. During the procedure the patient's oral temperature rose from 98 to 100°F. A progressive increase in blood flow was obtained. Fig. 15 shows the levels in each hand, averaged over five minute periods. At A the temperature in the plethysmograph water-bath was increased to 37°C to effect direct heating. The procedure was repeated five days after delivery. The control levels of hand flow after delivery were 13.7 ml in the left hand and 14.4 ml in the right compared with 23.0 ml and 34.9 ml respectively before delivery. Despite the lower initial levels, the blood flow in each hand 45 minutes after the onset of indirect heating was 45.0 ml, a level very similar to that obtained at the corresponding stage of the procedure before delivery. Thus, in both late pregnancy and the early puerperium, although hand blood flow was high, further increase could be obtained by release of vasoconstrictor tone.

SYMPATHETIC ACTIVITY

In most patients in the present series, towards the end of hand blood flow measurements, the effect of a sudden, unpleasant noise was observed. This acts as a nociceptive stimulus and usually results in vasoconstriction in the hand (Abramson and Ferris 1940). Owing to the variation in the actual levels of hand blood flow throughout pregnancy

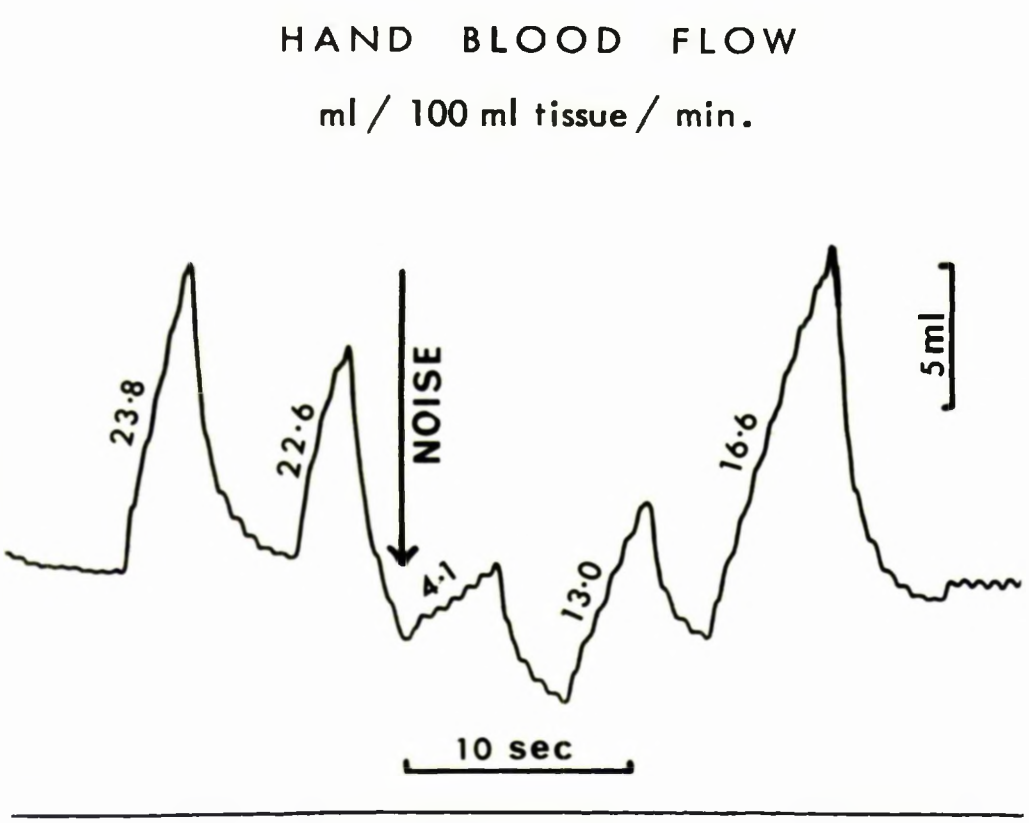


Fig. 16. Effect of sudden noise on hand blood flow. The subject, in late pregnancy, had a high resting hand flow.

the response was not assessed quantitatively. Fig. 16 shows the response obtained in a patient at a time of high hand flow. The brisk reduction in flow shows that sympathetic vasoconstriction is readily invoked. This vasoconstrictor effect was consistently present at all stages of pregnancy. Volume change in the fingers in response to noise and mental stress has been studied recently in pregnancy (Dolezal and Figar 1965). Compared with non-pregnant control subjects in whom constrictor responses were predominant, women in the early weeks of pregnancy (up to 12) showed a high proportion of dilator responses. As pregnancy progressed, the incidence gradually fell and the response became predominantly constrictor by term. The present study does not confirm this finding when the response of the whole hand is considered.

NATURE OF STIMULUS

The nature of the stimulus responsible for release of constrictor tone is not known. It is tempting to relate the change to the necessity of the mother to eliminate the heat produced by the placenta and foetus. The exact extent of the increase in basal metabolism in pregnancy is uncertain, although a figure of 15% mean increase has been found (Sontag, Reynolds and Torbet 1944) and is currently quoted (Guyton 1966). After assessing the available data, Hytten and Leitch (1964) conclude that the exact increase has not been measured satisfactorily. Oxygen consumption has been found to be increased by 9% in late pregnancy (Bader et al. 1955). However, it is doubtful if the

change in extremity blood flow is a direct effect of an increase in metabolism since, in hyperthyroidism, where there is a large increase in basal metabolism, increase in hand blood flow is not a constant feature (Shepherd 1963). Furthermore, Plass and Yoakum (1929) and Houssay (1955) state that if the metabolism of both the mother and baby are determined shortly after birth, the sum adds up to the figure found in the mother just before birth. If the increased metabolism in pregnancy were the primary stimulus for the increase in blood flow in the distal limb segments, we would expect a more abrupt reduction in flow after delivery. However, even if an increase in metabolism is not the primary stimulus, the effect undoubtedly involves a very efficient mechanism for heat loss. Not only is the increase in hand and foot blood flow essentially through a region with a large surface area, but the returning blood, passing along the superficial veins of the arm and leg has further opportunity for heat loss. Thus, considerable dissipation of heat can occur with a relatively small increase in total blood flow. The puerperium is still a metabolically active period and uterine involution and breast activity may be associated with considerable heat production and need for dissipation of heat.

The mechanism of temperature regulation in pregnancy seems to be a subject deserving further investigation. In the present study, measurement of oral temperature, using a clinical thermometer was close to normal in pregnancy but it is possible that a slight elevation of deep body temperature might occur in pregnancy. A more discriminating

method of measuring body core temperature would be required to establish this point.

EFFECT OF LACTATION

The specific influence of lactation on the "winding-down" processes following delivery has been studied inadequately. Early investigations into the change in basal metabolic rate in pregnancy and the puerperium (Sandiford and Wheeler 1924, Plass and Yonkam 1929) showed a rapid return to normal values soon after delivery and led these observers to conclude that lactation is not associated with an increased metabolism.

A recent study (Donovan, Lund and Hicks 1965) comparing plasma volume, red cell volume and body weight in the immediate puerperium and at six weeks after delivery, showed no difference between a group of women who were lactating and another who were not. This finding is in contrast to that found in cattle where lactation is associated with a relative increase in blood volume (Reynolds 1953). Differentation between lactating and non-lactating women does not seem to have been made in any of the other aspects of the haemodynamic changes in pregnancy referred to in the introductory sections.

The present study shows that lactation is not a direct factor in the maintenance of raised hand blood flow for some weeks after delivery.

SUMMARY AND CONCLUSIONS CONCERNING PERIPHERAL CIRCULATION IN HEALTHY, NORMOTENSIVE WOMEN WITH A SINGLE PREGNANCY

1. Peripheral vasodilatation in pregnancy in healthy, normotensive women occurs in the hand and foot but not in the forearm and calf.
2. The increase in hand and foot blood flow is sustained in the immediate puerperium and, in the hand, takes several weeks to return to normal levels. Lactation does not influence the return to normal.
3. Pulse rate is increased by 10 to 15 beats per minute in pregnancy.
4. There is no change in systolic blood pressure during pregnancy but there is a slight increase in diastolic blood pressure near term.
5. The total increase in extremity blood flow represents a small proportion of the increased cardiac output in pregnancy.
6. Differences between the present results and those previously reported, particularly related to forearm blood flow, may be due to important technical differences.
7. While the increase in blood flow to the distal segments of the extremities serves to dissipate increased heat production, the precise mechanism is not established. It is suggested that the vasodilatation is mediated by the release of vasoconstrictor sympathetic tone rather than by the direct action of a humoral vasodilator substance.
8. Release of vasoconstrictor tone is not complete, even in late pregnancy.

RESULTS IN MULTIPLE PREGNANCY - NORMOTENSIVE WOMEN

Studies were made in 12 women with twins and in 2 with triplets. These patients correspond to Numbers 53 to 66 in the total series and clinical details are given in Table B in the Appendix. Of the women with twins, three were multigravidae. Both sets of triplets were uniovular.

Measurements were made at times varying from 26 weeks of gestation to after delivery. Most patients were attending as out-patients although some were resting in the antenatal ward from 30-34 weeks. Although pregnancy was otherwise uncomplicated, only two women had spontaneous vaginal deliveries. Caesarean section was performed in two patients on account of prolonged labour and on another two on account of malpresentations. The remaining patients had operative vaginal deliveries. The average weight of the babies in the twin pregnancies was 5 lb. 10 ozs. All the babies survived except the second twin of patient No. 55 in whom foetal distress and uterine inertia developed after the birth of the first child. Internal version and breech extraction was performed but the baby was asphyxiated and died 10 hours after delivery. Owing to the high rate of operative delivery, puerperal studies had to be omitted in some patients. Prolonged follow-up of this group of women was unrewarding owing to their domestic committments.

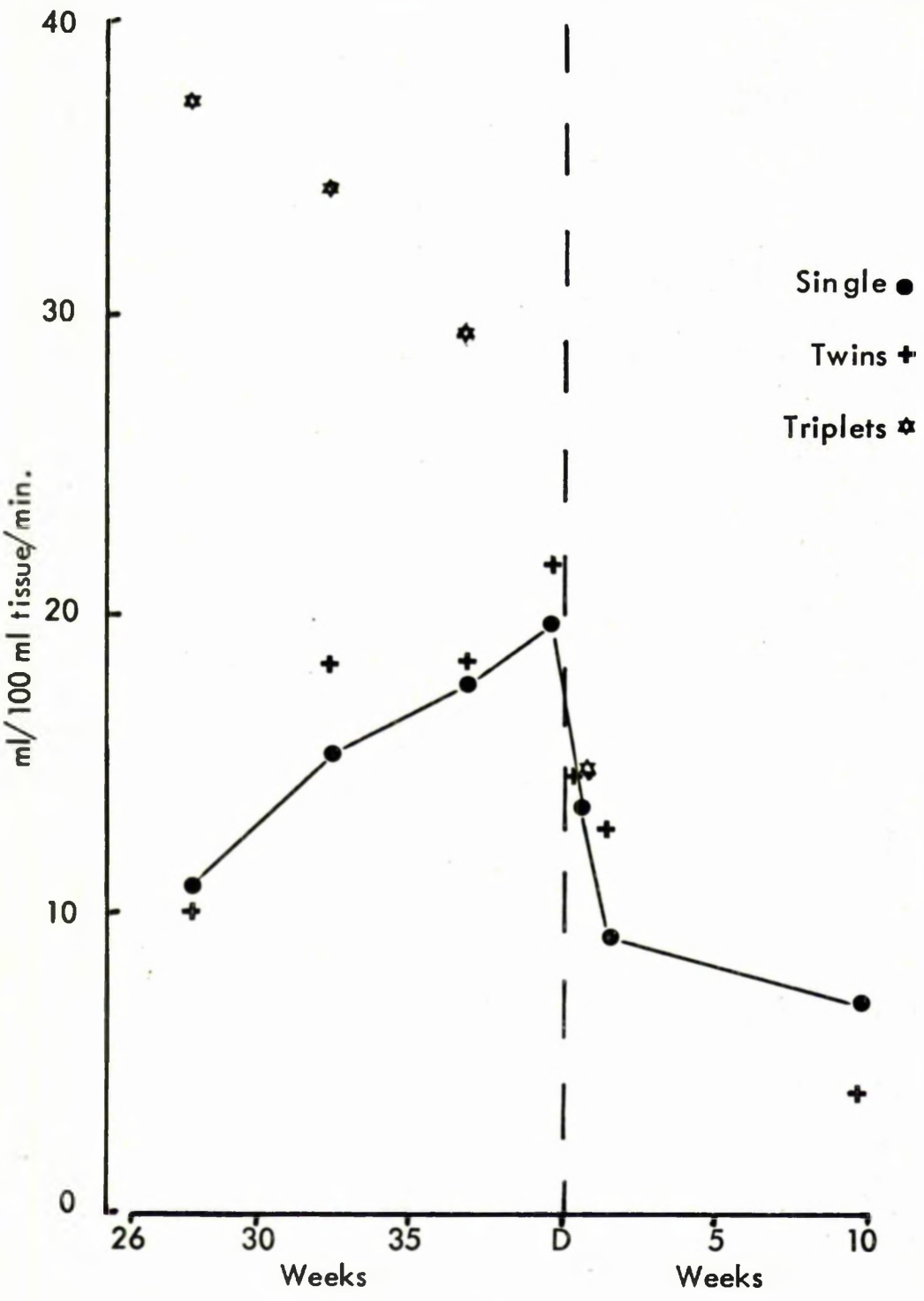


Fig. 17. Mean hand blood flow in multiple pregnancy in the third trimester and after delivery. The values for single pregnancy are given for comparison.

HAND BLOOD FLOW

Table IX gives the results obtained from 38 recordings of hand blood flow in these 12 women with twins and 7 recordings in the 2 with triplets. The mean values are shown in Fig. 17 in relation to those obtained in normotensive women with a single pregnancy.

TABLE IX - HAND BLOOD FLOW - NORMOTENSIVE MULTIPLE PREGNANCY

ml/100 ml tissue/min

TWINS	WEEKS OF PREGNANCY				AFTER DELIVERY		
Patient Number	26-30	31-34	35-38	39-D	D-7 days	8-14 days	9 weeks +
53			22.1	15.3		19.0	
54		25.0	17.2	20.4			
55		30.4	23.4	31.8			
56		9.9	6.5				
57			20.2	34.2		5.3	
58		17.4	17.1		23.6	20.3	3.5
59	9.3			12.1	13.0		4.2
60	11.6	22.0			12.6*		
61		9.3			6.7		
62	9.5				18.8		
63		13.9	27.2	32.6			
64			14.0	4.6		6.9	4.3
MEAN	10.1	18.5	18.2	21.6	14.9	12.9	4.0
TRIPLETS							
65		15.9*	29.6		7.4		
66	37.4	52.6			22.4		

* average of more than one recording.

When the earliest recordings were made (26 to 30 weeks) the level of blood flow was close to that obtained in single pregnancy, but from then onwards the mean level was slightly higher. It was not possible, however, to show that the increase in flow was statistically significant ($p < 0.01$) at any one stage, the variation between patients being large. The levels obtained in the puerperium differed little from those found in single pregnancy.

The findings in the two patients with triplets are of interest. One (No. 66) had a very high level of hand blood flow - 52.6 ml at 31 weeks of pregnancy. Unfortunately, premature labour at 32 weeks prevented subsequent recordings. Labour and delivery were relatively easy with no anaesthesia. A further recording 30 hours after delivery showed a substantial reduction in hand flow - 22.4 ml. Further observations were precluded by the development of an allergic rash on the third puerperal day.

FOOT BLOOD FLOW

Measurement of foot blood flow was made on 30 occasions in 10 of the women with twins and on 3 occasions in 1 with triplets. Table X gives the values subdivided according to gestation and Fig. 18 shows the mean values in relation to single pregnancy. As in the hand, there was an increase in the mean flows after 30 weeks of pregnancy. Despite considerable scatter of individual readings in late pregnancy, the increase in flow was more consistent than in single pregnancy. However, a t-test carried out on the mean values obtained at 35 to

38 weeks showed that the increase compared with single pregnancy at the same stage was not significant ($t = 1.3$, $p > 0.2$). There was a marked increase in foot flow in the one patient with a triplet pregnancy.

TABLE X - FOOT BLOOD FLOW - NORMOTENSIVE MULTIPLE PREGNANCY

ml/100 ml tissue/min

TWINS	WEEKS OF PREGNANCY				AFTER DELIVERY		
Patient Number	26-30	31-34	35-38	39-D	D-7 days	8-14 days	9 weeks+
53			6.9	5.5		10.9	
54		6.9	7.9	7.8			
55		9.7	15.3	8.2			
56		2.7					
57			3.3	7.1		1.6	
58		7.5	4.0		5.6*		2.4
59	4.4				5.7		2.4
61		2.3			3.1		
63		3.5	10.3	9.6			
64			6.2	3.6		2.8	1.1
MEAN	4.4	5.4	7.7	7.0	4.8	5.1	2.0
TRIPLETS							
66	13.7	20.8	-	-	13.3		

* average of more than one recording.

FOREARM BLOOD FLOW

Table XI gives the results of 26 recordings in 10 of the patients with twins and 6 in the 2 with triplets. Fig. 19 shows the mean values. Again, after 30 weeks gestation there was some increase in forearm flow

NORMOTENSIVE WOMEN - MULTIPLE PREGNANCY

MEAN FOREARM FLOW

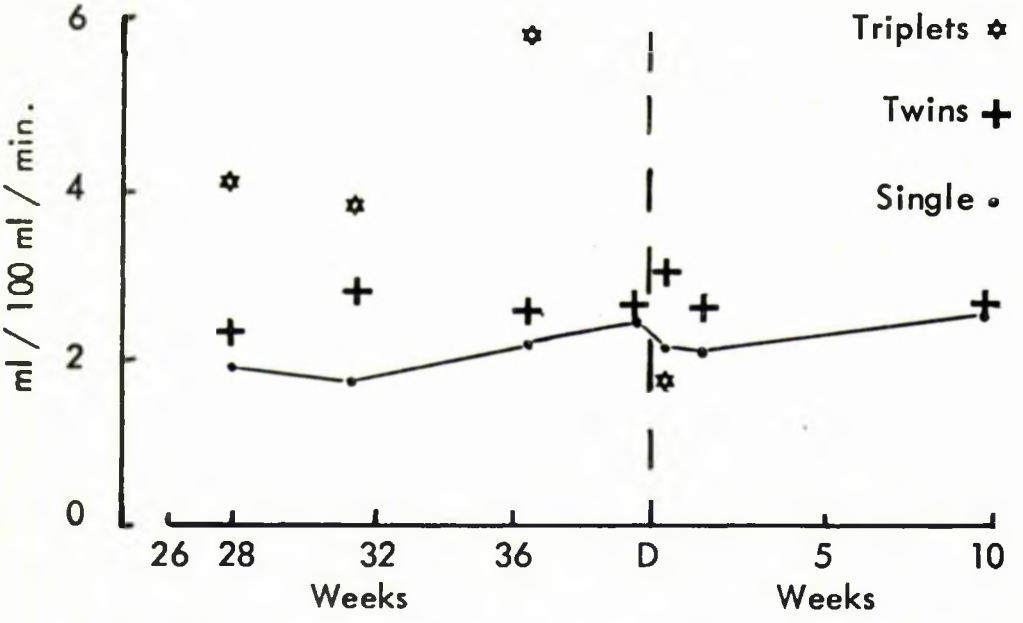


Fig. 19. Mean forearm blood flow in multiple pregnancy in the third trimester and after delivery.

MEAN CALF FLOW

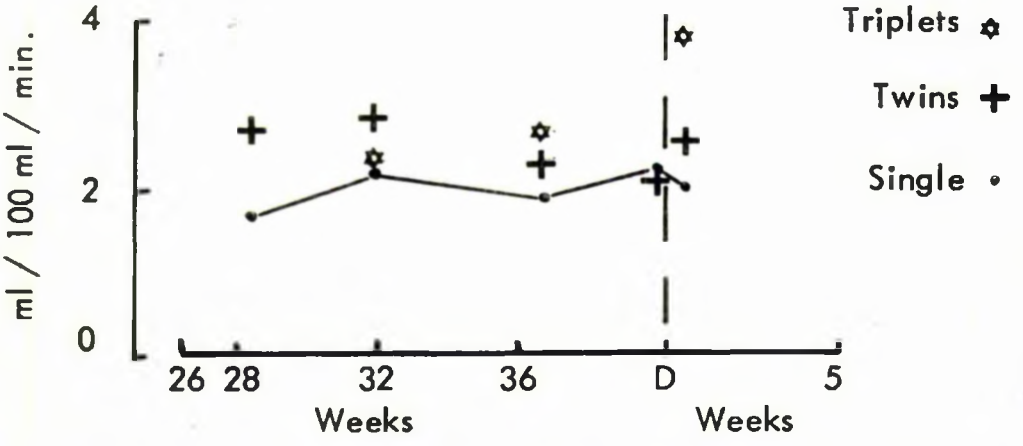


Fig. 20. Mean calf blood flow in multiple pregnancy in the third trimester and after delivery.

TABLE XI - FOREARM BLOOD FLOW - NORMOTENSIVE MULTIPLE PREGNANCY

ml/100 ml tissue/min

TWINS	WEEKS OF PREGNANCY				AFTER DELIVERY		
Patient Number	26-30	31-34	35-38	39-D	D-7 days	8-14 days	9 weeks+
53		5.1	2.4	3.2	2.6		
54		2.2	3.6	4.0			
55				4.4			
56		2.2					
57			1.3	1.3			
59		1.9		1.9		2.6	2.6
60	2.0	2.8			3.3*		
61			1.8		1.4		
62	2.6				4.9		
63		2.6	3.8	1.7			
MEAN	2.3	2.8	2.6	2.7	3.0	2.6	2.6
TRIPLETS							
65		4.2	5.8		1.4		
66	4.1	3.5			2.0		

* average of more than one recording.

compared with single pregnancy. A t-test on the means obtained at 31 to 34 weeks in twin and single pregnancy (when the difference was greatest) showed that the increase is not significant ($t = 2.02$, $p > 0.05$).

The measurements in pregnancy on the two women with triplets showed forearm blood flow levels raised to those rarely found in the normotensive women with a single pregnancy. In the puerperium, the levels were similar to those found in single pregnancy.

CALF BLOOD FLOW

Table XII gives the values obtained in 12 measurements on 4 of the women with twins and 4 recordings in the 2 with triplets. Fig. 20 illustrates the mean values in relation to single pregnancy. There is a slight tendency to an increase in mean calf flow in the studies made. The individual results are, however, within the range found in single pregnancy.

TABLE XII - CALF BLOOD FLOW - NORMOTENSIVE MULTIPLE PREGNANCY
ml/100 ml tissue/min

TWINS	WEEKS OF PREGNANCY				AFTER DELIVERY
Patient Number	26-30	31-34	35-38	39-D	D-7 days
54		3.3*	3.5		
57			1.5	1.8	
60	2.6	2.9			2.4*
63		1.9	1.5	2.2	
MEAN	2.6	2.7	2.2	2.0	2.4
TRIPLETS					
65		2.2	2.5		5.3
66					2.1

* average of more than one recording.

PULSE RATE

As in women with a single pregnancy, the pulse rate was recorded during the blood flow measurements. Table XIII gives the rates obtained.

Comparison with those obtained in women with a single or a hypertensive pregnancy is made in Table XXII (p. 105). The mean values and range are essentially similar to those obtained in single pregnancy.

The pulse rates obtained in the two patients with triplets are also shown in Table XIII. There is no consistent increase.

TABLE XIII - PULSE RATE - MULTIPLE PREGNANCY

TWINS	WEEKS OF PREGNANCY						WEEKS AFTER DELIVERY			
Patient Number	Under 30	31-32	33-34	35-36	37-38	39-D	D-1	1-2	3-8	9+
53			85	71	60*	65	75	60		
54		104	94*	100	94					
55			105	100		77				
56		86	100							
57				78	68*					
58			72		70		69*			68
59	90	92				96	92	88		64
60	96	112					110			
61			86	89			73			
62	90				72		78			
63			80	89*		91				
64				72	70			81		72
MEAN	92	99	89	86	72	82	83	76		68
TRIPLETS										
65		70	70*	73			81			
66	101	92					80			

* average of more than one occasion.

SUMMARY OF RESULTS IN NORMOTENSIVE WOMEN WITH MULTIPLE PREGNANCY

From these results, in twin pregnancy, it is clear that in all limb segments studied, there is a slight increase in mean blood flow after 30 weeks of pregnancy. The individual values are, however, within the range obtained in normotensive women with a single pregnancy.

In two patients with triplets, there was an increased tendency to vasodilatation in all segments.

The pulse rate is not increased in multiple, compared with single pregnancy.

DISCUSSION

Surprisingly, few of the investigations into the changes in haemodynamics in pregnancy contain any reference to multiple pregnancy. At the start of this investigation even such a basic measurement as pulse rate did not seem to have been specifically observed in twins. It seems probable that where there are two or more foetuses, some differences, either qualitative or quantitative, might occur compared with single pregnancy. Study of any observed differences might help in elucidating the nature of the normal circulatory adaptations.

In their measurement of uterine blood flow, Metcalfe and his co-workers (1955) included one patient with twins and estimated uterine blood flow to be approximately 1000 ml compared with 500 ml in single pregnancy.

Recently, Rovinsky and Jaffin (1965) have measured blood volume in both single and multiple pregnancy. Compared with non-pregnant control subjects, increases in plasma volume in late pregnancy were 48% and 67% respectively. Red cell and total blood volume increases were more variable but showed a corresponding tendency to a greater increase in twins. In two women with triplets the levels were considerably higher.

These findings have not, however, been confirmed by Pritchard (1965) who found no difference in blood volume or red blood cell volume between single and multiple pregnancy. Rovinsky and Jaffin (1966) have extended their investigation to include cardiac rate, cardiac

index, stroke volume, circulation time and central blood volume in multiple compared with single pregnancy. Heart rate was unchanged in twin compared with single pregnancy except for the final weeks (37 - 40) of pregnancy, when a rate of 115 beats per minute was obtained compared with 98 in single pregnancy near term. Reference to their earlier paper (Rovinsky and Jaffin 1965) suggests that the mean pulse rate value in late twin pregnancy was based on 7 recordings. Since these pulse rates were recorded at the time of cardiac output and blood volume estimations it is doubtful if the subjects were in a resting state. A mean pulse rate of 81 beats per minute in non-gravid control subjects under the same experimental conditions suggests that this might have been so. Restlessness on lying still was a frequent finding in multiple pregnancy in the present series tending to become worse in late pregnancy, so that despite the relative comfort of the technique for the patients the procedure was abandoned in some cases. Similar restlessness in Rovinsky and Jaffin's patients might have accounted for the rise in pulse rate only in the final weeks of twin pregnancy.

Rovinsky and Jaffin (1966) found an increase of approximately 10% in cardiac index in twin compared with single pregnancy at the corresponding stage of gestation. Otherwise, mean stroke volume and mean circulation time changed to the same degree as in single pregnancy. The increase in cardiac output despite no alteration in arterial blood pressure denotes a relative reduction in total peripheral resistance. However, the authors' assumption that this decrease in resistance is

entirely uterine and is disproportionately high compared with the volume increase of the uterine vascular bed does not seem warranted in the absence of adequate measurements of uterine blood flow and of the distribution of blood flow to other organs in multiple pregnancy. The present findings indicate that although there is a slight increase in mean blood flow through the extremities in twin pregnancy on average this represents a negligible proportion of the increase in cardiac output.

The studies on triplet pregnancy are too few to draw definite conclusions from but suggest that not only is there increased hand and foot vasodilation but a vasodilator mechanism in the forearm is also being invoked.

NORMOTENSIVE WOMEN WITH SYSTEMIC DISORDERS

Details of patients in this group are given in Table C in the Appendix. The systemic disorders preceded the onset of pregnancy; both diabetic patients were maintained on insulin. The patient with spontaneous hypoglycaemia (No. 71 in the series) developed episodes of severe hypoglycaemia during the early months of pregnancy. Laparotomy, at 20 weeks of pregnancy, revealed no definite islet cell tumour. Part of the pancreas was excised and showed some islet cell hyperplasia. Thereafter her condition was improved but not entirely cured. The final patient in this group (No. 72) had had both adrenal glands removed six and three years respectively before her pregnancy for hyperadrenalism and was maintained subsequently on prednisolone therapy.

Table XIV shows the levels of blood flow in the limbs studied, at the stages of pregnancy indicated. The wide variation in levels of hand flow obtained in the series of healthy women makes interpretation of individual cases difficult but there was a rise in hand flow in late pregnancy in all the women studied except in the patient with spontaneous hypoglycaemia. Foot blood flow was measured in the diabetic patients and was elevated in late pregnancy.

There was no alteration in forearm or calf blood flow in these patients.

TABLE XIV - LIMB BLOOD FLOW IN NORMOTENSIVE WOMEN WITH SYSTEMIC DISORDERS

ml/100 ml tissue/min

PATIENT Number	CONDITION	STAGE OF PREGNANCY (WEEKS)	HAND	FOOT	FOREARM	CALF
67	MITRAL STENOSIS	10	2.1			2.5
		16	4.3		2.8	1.4
		27	26.7		3.0	1.6
		38	19.1	2.8		
68	AORTIC STENOSIS	32	10.9			
		40	30.2			
		D + 1	24.6			
		D + 8	9.5			
69	DIABETES	35	12.6	6.3	0.9	1.4
		36	17.0			1.6
		D + 6	2.0			
70	DIABETES	20	6.5		0.9	1.5
		22	3.0		0.5	1.3
		30	5.6		1.9	2.1
		34	16.8	6.0	4.1	1.5
		36		6.3	2.0	1.7
		D + 2	15.9	8.1		
		D + 3	7.6			3.5
		D + 5	11.5		2.5	
		D + 9	10.0		1.7	
		D +13	5.0		4.1	
71	SPONTANEOUS HYPO-GLYCAEMIA	10	5.7		2.3	1.5
		29	5.2		2.0	2.5
		33	5.7		1.6	1.7
		35	6.2		2.4	2.3
		D + 1	14.8		1.9	0.7
72	POST-ADRENAL-ECTOMY	38	16.2		1.8	2.9
		D +) 1 year +)	7.5		2.0	2.2

NORMOTENSIVE WOMEN WITH OBSTETRIC DISORDERS

During the studies on the group of healthy women complications of pregnancy developed in several leading to their exclusion from the 'normal' group. Table D gives details of 3 of these women (Nos. 73-75), where several readings were obtained and were carried into the puerperium. Table XV gives the blood flow levels in the different segments. The pattern of change is similar to that found in normal pregnancies.

TABLE XV - LIMB BLOOD FLOW - NORMOTENSIVE OBSTETRIC DISORDERS

ml/100 ml tissue/min

PATIENT NUMBER	CONDITIONS	STAGE OF PREGNANCY (WEEKS)	HAND	FOOT	FOREARM	CALF
73	DYSMATURE BABY	34	4.5		1.8	3.3
		38	11.4	3.0	2.0	1.7
		D + 1 day	5.1		1.6	
		D + 1 week			2.1	3.2
74	REVEALED ACCIDENTAL HAEMORRHAGE	37		13.3		
		D + 1		7.8		
		D + 11		2.6		
75	TWINS ONE I.U.D. at 34 weeks	30	7.8	2.9	4.1	
		33				1.5
		35	15.8	2.2		2.4
		37	16.0	2.0	2.1	2.1
		D + 6			4.6	

I.U.D. - Intra-uterine Death.

HYPERTENSIVE PREGNANCY

Similar measurements of limb blood flow have been carried out in 54 women with a raised blood pressure in pregnancy. Most of these women had regular antenatal care from early in pregnancy. Some had a normal blood pressure in early pregnancy and clearly developed toxaemic hypertension as pregnancy progressed, some were known to have hypertension before the pregnancy began, some were hypertensive in early pregnancy but normotensive during the mid-trimester with a rise near term and a few appeared beyond mid-pregnancy with no earlier records but with a raised blood pressure.

CLASSIFICATION OF HYPERTENSIVE WOMEN IN PREGNANCY

In order to sub-divide this obviously hetergeneous group, the following criteriae were used to group the patients. Classification was retrospective and in some instances could not be made until after the post-natal visit. Any sub-division of hypertensive women in pregnancy is necessarily arbitrary. The definitions used in the present study are those operative in the obstetric unit at Charing Cross Hospital. Those with essential hypertension or severe toxaemia are referred for renal investigation following delivery.

1. TOXAEMIA

a) Mild - This was defined as a rise in diastolic blood pressure to 90 mm Hg or over on at least two occasions in the last trimester of pregnancy

The 15 patients in this group correspond to Nos. 76 to 90 in the total series and details are given in Table E in the Appendix. Their ages ranged from 19 to 34 years. Eleven were primigravidae. Of the four parous women, three had a history of mild toxaemia in a previous pregnancy. All the patients booked before 24 weeks, were normotensive then and had regular ante-natal care except for one (No. 83) who did not book until 34 weeks but who had a blood pressure of 115/80 at that time. All pregnancies reached 38 weeks gestation and no patient had hypotensive therapy at any stage. Labour was spontaneous, near term in 3 patients and was induced in the remaining 12: by artificial rupture of the membranes in 7, pitocin in 3 and by both methods in the other 2. None in this group had persistent proteinuria. All had live births and the average weight of the babies was 6 lb. 10 ozs.

b) Severe - This was defined as:-

A rise in diastolic blood pressure to 100 mm Hg or above on at least two consecutive days as an in-patient at rest, or

A rise in diastolic blood pressure to 90 mm Hg or above on at least two consecutive days as an in-patient at rest together with proteinuria in at least two non-infected mid-stream specimens of urine.

The 16 patients in this group, whose ages ranged from 18 to 38 years, correspond to Nos. 91 to 106 in the total series. Details are given in Table F in the Appendix. Eleven were primigravidae. One had had a hysterotomy for fulminating toxaemia, two had a previous history of toxaemia and the remaining two parous women were not known

to have had toxaemia. Thirteen booked before 24 weeks, were normotensive and had regular ante-natal care. Three of this group (Nos. 96, 99 and 100) were admitted to hospital after 30 weeks of pregnancy because of a rise in blood pressure and recordings of the blood pressure in early pregnancy were not available. Since all developed proteinuria and had a blood pressure below 140/90 mm Hg six weeks after delivery, they were classified in the toxaemia group. One patient (No. 105) who developed toxaemia at 29 weeks was studied from 8 weeks of gestation. All the pregnancies were terminated between 29 and 39 weeks: two by elective Caesarean section, six by artificial rupture of the membranes, two by pitocin only, five by both these methods of induction and one, who had an intra-uterine death at 35 weeks of pregnancy, had labour induced by injection of hypertonic saline into the amniotic sac. The average weight of the babies was 5 lb. 6 ozs. Apart from the intra-uterine death referred to above, there were two neo-natal deaths: patient No. 95 whose baby at 36 weeks of gestation weighed 2 lb. 14 ozs. and died on the 5th day, and patient No. 101 who had an elective Caesarean section at 29 weeks for severe toxaemia and whose baby, weighing 3 lb. 3 ozs, died of hyaline membrane disease on the second day. All the patients in this 'severe toxaemia' group had proteinuria. Two (Nos. 92 and 106) were given a hypotensive drug (10-methoxy deserpidine - "Decaserpyl") at some stage.

2. <u>ESSENTIAL HYPERTENSION</u>

This was defined as a diastolic blood pressure of 90 mm Hg before

24 weeks of pregnancy, recurring on at least three separate occasions antenatally and still persisting at the post-natal visit.

The 17 patients in this group, whose ages ranged from 23 to 41 years, correspond to Nos. 107 to 123 in the total series (Table G in the Appendix). Of five who were pregnant for the first time, one was known to have had hypertension before the pregnancy began. Of the others, one had had a previous abortion, another three abortions and one patient (No. 123) had had two previous hysterotomies for fulminating super-imposed toxaemia. The remaining nine parous patients were all known to have had an elevation of blood pressure during a previous pregnancy. All the patients in this group booked before 24 weeks of pregnancy and had regular ante-natal care. Pyelonephritis had been diagnosed in one patient (No. 114) and hydronephrosis in another (No. 115) before the onset of pregnancy. Four of the group (Nos. 113, 117, 118 and 123) were on a hypotensive drug for part of the pregnancy and one patient (No. 111) was on α-methyldopa before, throughout and after the pregnancy.

Four of the patients in this group went into labour spontaneously near term. Pregnancy was terminated in the others between 34 and 40 weeks: in four by elective Caesarean section and by artificial rupture of the membranes in the other nine. Of these, three had pitocin in addition but two failed to go into labour and required Caesarean section. Thus, the operative delivery rate was high and puerperal studies were precluded in some. All the babies survived and the average weight was 6 lb. 12 ozs.

3. HYPERTENSION AND SUPER-IMPOSED TOXAEMIA

Studies were carried out on four women (Nos. 124 - 127) who had hypertension according to the previous criteriae but who also developed persistent proteinuria. All were parous and were known to have been hypertensive during their previous pregnancy. Clinical details are given in Table H in the Appendix. The development of proteinuria was usually accompanied by an increase in hypertension and by oedema. Two (Nos. 124 and 127) were treated with hypotensive drugs at some stage. Spontaneous labour occurred in one at 37 weeks. Labour was induced by membrane rupture in two, one of whom required Caesarean section for a subsequent malpresentation. The remaining patient had an elective Caesarean section at 34 weeks. The baby, who weighed 3 lbs, developed respiratory distress and died at 7 weeks. The other three babies survived.

4. TWINS WITH SUPERIMPOSED TOXAEMIA

Two subjects (Nos. 128 and 129), both primigravid, developed toxaemia of mild degree according to the above criteriae (Table I in the Appendix). Pregnancy was terminated at 38 weeks and one required Caesarean section on account of a prolonged labour. The babies all survived.

RESULTS - LIMB BLOOD FLOW IN HYPERTENSIVE PREGNANCY

As in normotensive women, limb blood flow was calculated and expressed in ml per 100 ml tissue per minute, the mean value on each occasion being obtained by taking the average flow over several minutes in a steady state.

Measurements were made in the total of 54 patients on 552 occasions. The results are sub-divided according to the limb studied and the duration of pregnancy within the diagnostic groups previously described. It was not practicable to study all limbs in every subject. A systematic effort was made to study forearm blood flow in all hypertensive patients since the initial measurements on normotensive women indicated that no gross change in forearm flow was occurring in pregnancy and that there was less variability between subjects than in, for example, the hand. Differences between normotensive and hypertensive subjects would therefore be more readily detected. Hand, foot and less frequently calf flow were measured in patients with severe toxaemia or essential hypertension. A few studies in segments other than the forearm were made in women with mild toxaemia since, at the earliest rise in blood pressure, the eventual severity of toxaemia was not known. In severe toxaemia, the results before 24 weeks of pregnancy refer to patient No. 105 who was studied from 8 weeks of pregnancy. Otherwise, the results in the severe toxaemia group refer to patients studied after a rise in blood pressure had occurred although the severity was not necessarily established. In the group with mild

toxaemia, two subjects (Nos. 82 and 90) were studied before the onset of toxaemia and in the Tables, results before 38 weeks include these two patients who were normotensive at the time of measurement. When a limb segment flow was measured on more than one occasion within the period indicated in each table, the average is recorded and these readings are indicated. Patients on hypotensive therapy at any stage are indicated (+) but any recordings made during or within two weeks of hypotensive therapy are excluded from the main group and are recorded separately. As in normotensive pregnancy, puerperal studies were not carried out for at least four days after an operative delivery or when pyrexia was present. Any patient who required heavy sedation or who was ill from any intercurrent cause was also omitted. Patients studied had not been given a sedative drug within four hours of the start of the investigation.

The results for each limb studied are given in Tables XVI to XXI according to the diagnostic group. Since studies were carried out more frequently, in the last trimester of pregnancy than in normotensive pregnancy, the results of individual patients are given in two weekly periods. Figs. 21 to 24 give the mean values for each limb for those with severe toxaemia and essential hypertension in comparison with normotensive pregnancy.

TABLE XVI - LIMB BLOOD FLOW IN MILD TOXAEMIA

ml/100 ml tissue/min

a) HAND	WEEKS OF PREGNANCY								WEEKS AFTER DELIVERY			
Patient Number	Under 24	25-28	29-30	31-32	33-34	35-36	37-38	39-D	0-1	1-2	3-8	9+
78								9.4	3.1			
80								7.9				
86								14.8	18.9			
89						15.7						7.6
90	12.1*				11.3		28.5	21.3				
MEAN	12.1*				11.3	22.1		13.3	10.9			7.6
b) FOOT												
89						3.1						1.9
90	2.8*				2.9		8.5	3.0	5.6			
c) FOREARM												
76						3.5			3.9	4.1		
77			3.7	2.4		2.8	2.7		3.3			
78								3.0	2.0			
79						1.4		1.8		1.6	1.4	
80								1.5				
81							3.4		2.8			
82	2.4					2.2						3.9
83					2.0		1.4			2.2		
84							2.8			2.0		
85							2.6					
86								1.9	1.8			
87						4.7		1.9	2.7		1.8	1.8
88					1.5		1.1	1.9	1.7		2.8	2.2
89			2.1	2.4			1.2		1.9	3.1	2.2	1.8
90	2.1*	2.5		2.4			1.8	2.1	2.5		2.1	
MEAN	2.2	2.8		2.1		2.4		2.0	2.5	2.6	2.1	2.4

* Average of 3 occasions in 1 patient.

TABLE XVII - LIMB BLOOD FLOW IN SEVERE TOXAEMIA

ml/100 ml tissue/min

a) HAND	WEEKS OF PREGNANCY								WEEKS AFTER DELIVERY			
Patient Number	Under 24	25-28	29-30	31-32	33-34	35-36	37-38	39-D	0-1	1-2	3-8	9+
93				7.2					30.0	16.3		
94						9.6	7.8		3.8			7.3
95							13.0		11.5*			6.9
97								14.6	16.8	9.7		10.6
98			22.6		16.5							
99			2.8	11.3	16.1	25.8*			3.6			
100						22.9						
102							17.7		4.6		5.9	
104							11.7					5.3
105				8.6						2.7		5.1
106												3.5
MEAN			12.7		11.9		15.5	14.6	11.7	9.6	5.9	6.6
b) FOOT												
93				1.8					4.2	1.9		
94							2.2		1.5			2.9
95							3.6					2.1
97								2.7	3.7			1.8
98		4.1				1.2						1.3
99				3.3		6.3			2.5			
100						3.2						
102							3.1		2.1		5.3	
104							1.0					1.4
105	2.5											3.9
MEAN	2.5	4.1		2.6		2.9		2.7	2.8	1.9	5.3	2.2

* Average of more than one recording.

TABLE XVII (contd.)

c) FOREARM	WEEKS OF PREGNANCY								WEEKS AFTER DELIVERY			
Patient Number	Under 24	25-28	29-30	31-32	33-34	35-36	37-38	39-D	0-1	1-2	3-8	9+
91		1.8	3.2	2.7		3.2		3.5				
92+									3.0			2.9
93				5.7					5.1	4.2		
94						2.0			2.2			2.9
95							3.6		1.3			2.1
96						2.0	3.0		2.1			
97								2.5	1.5			1.6
98						1.6						2.0
99			1.9		2.2	1.8*			2.1			
101			6.9							1.7	4.1	3.2*
102						1.6	1.3		2.8		2.4	
103						2.4	2.5		2.0			
104							1.0			1.4		2.2
105	3.1*	2.4	1.9	1.1						3.0		3.2
106+										3.6	2.3	
MEAN	3.1	3.7		2.9		2.2		3.0	2.5	2.8	2.9	2.5

d) CALF	WEEKS OF PREGNANCY		WEEKS AFTER DELIVERY
Patient Number	35 - 36	37 - 38	9+
95		1.8	2.2
100	3.3		
106		2.6	3.2

* Average of more than one recording.

\+ Values omitted when on hypotensive drug.

TABLE XVIII - LIMB BLOOD FLOW IN ESSENTIAL HYPERTENSION

ml/100 ml tissue/min

a) HAND	WEEKS OF PREGNANCY								WEEKS AFTER DELIVERY			
Patient Number	Under 24	25-28	29-30	31-32	33-34	35-36	37-38	39-D	0-1	1-2	3-8	9+
107							12.2		5.4			
108	10.1							29.1				
109					19.4	10.7						
110								16.8	10.1	6.3	8.5	
112	6.1	2.9		9.5	27.3	19.7	17.5		17.1		5.5	
113+			10.5*								4.3	
114				16.1	12.7	31.5	30.2	28.4	21.1*	14.9*	6.0*	2.8
115		13.5			21.8		31.2*		16.8*			5.7
116		2.9	4.5					23.5	16.4		6.8	
118+					8.2							
119				3.5		4.4			5.9			
120						4.6						6.3
122	6.8	10.2	8.9				17.6	21.3				5.2
MEAN	7.7	7.6		14.8		18.0		23.8	13.3	10.6	6.2	5.0
b) FOOT												
107							6.9		1.9			
108	1.9											
112	1.5	3.8		1.8	3.9	4.1	2.8*		4.1		4.4	
113+			4.7	7.6							2.8	
115					7.6	5.0	3.0					
116		1.6	2.5					6.8			4.3	
117+	3.8											
119				2.7		2.8	7.2		6.1			
120						2.3			2.9			3.2
122		2.2	2.2				5.6	9.3	3.6			1.6
MEAN	2.4	2.8		4.7		4.4		8.0	3.7		3.8	2.4

+ Values omitted when on hypotensive drug

* Average of recordings on more than one occasion

TABLE XVIII (contd)

c) FOREARM	WEEKS OF PREGNANCY								WEEKS AFTER DELIVERY			
Patient Number	Under 24	25-28	29-30	31-32	33-34	35-36	37-38	39-D	0-1	1-2	3-8	9+
107						1.6	1.2		2.4			
108	1.2		1.8		1.3		1.9	1.9				
109					2.2	3.4						
110								3.2		1.9		2.4
112	1.6	2.3		2.7	1.8	2.9	1.6		1.2		2.4	
113+			2.5*								2.2	
114				2.2		1.7	1.9	1.7	2.1*	1.8*	3.5	1.4
115		2.0			2.5		4.1*		1.5			2.2
116		3.2	2.7		1.5			2.2	2.0		2.9	
117+	2.5											
118				3.3*								
119				1.9		3.0	4.5		2.9			
120							3.8			4.2		5.3
121								1.9		2.3		2.7
122		5.6		1.7	2.3		1.4	2.3	2.3		2.0	2.2
123+				1.5			2.7			4.0		4.9
MEAN	1.8	2.9		2.1		2.5		2.2	2.1	2.8	2.6	3.0
d) CALF												
108			1.6					1.6				
110								0.8		1.2	2.5	
112							1.3		1.6			
114				2.7	1.9	1.6			2.0*	1.5*	3.3	2.3
115		1.8			2.2		2.5*		1.1	2.5		1.4
116		1.7		1.3				2.7	2.4			
117+	1.4											
119						2.6						
122	1.2	2.7							3.6			
MEAN	1.3	2.0		2.0		2.0		1.7	2.1	1.7	2.9	1.9

+ Values omitted when on hypotensive drug

* Average of recordings on more than one occasion

TABLE XIX - LIMB BLOOD FLOW IN HYPERTENSION WITH SUPERIMPOSED TOXAEMIA

ml/100 ml tissue/min

a) HAND	WEEKS OF PREGNANCY								WEEKS AFTER DELIVERY			
Patient Number	Under 24	25-28	29-30	31-32	33-34	35-36	37-38	39-D	0-1	1-2	3-8	9+
124+				6.4	10.4						5.0	
125									4.1	7.9		
126	4.3*		1.7	15.0	27.7*					10.5		11.9
127+	2.0	7.5	8.6*	10.8*	15.2	8.3	24.8	23.8	27.1	18.8	14.8	5.2*
MEAN	3.1	5.9		14.2			19.0		15.6	12.4	9.9	8.5
b) FOOT												
126	1.7*		1.4	2.5	6.4					2.2		
c) FOREARM												
124+			1.4	1.1					1.9		2.6	
125									2.4	1.9		
126	2.7*		2.1	1.8	4.0*					2.5	2.2	2.5
127+	1.9	1.3	0.8*	2.6*		2.2		1.6		2.7	2.7	2.0
MEAN	2.3	1.4		2.4			1.9		2.3	2.4	2.5	2.3
d) CALF												
126	2.4	1.7	2.4	2.8	4.6					1.6		3.3
127+	3.4	1.4	1.5	1.0	1.3	1.4	1.0	1.0		1.7	2.1	2.3
MEAN	2.9	1.7		2.4			1.2			1.6	2.1	2.8

+ Values omitted when on hypotensive drug

* Average of more than one recording

TABLE XX - LIMB BLOOD FLOW IN TWIN PREGNANCY WITH MILD TOXAEMIA - 2 PATIENTS

LIMB	Patient Number	WEEKS OF PREGNANCY					WEEKS AFTER DELIVERY	
		31-32	33-34	35-36	37-38	39-D	0-1	3-8
a) HAND	128	13.5		7.4				1.9
	129		39.6		22.4		3.3	
b) FOOT	128				8.5			1.9
	129		9.8		5.8		1.4	
c) FOREARM	128		2.5	2.5	1.1			1.3
	129	1.8	1.7	2.3			1.6	

TABLE XXI - LIMB BLOOD FLOW IN WOMEN ON HYPOTENSIVE THERAPY

a) HAND	WEEKS OF PREGNANCY								WEEKS AFTER DELIVERY			
Patient Number	Under 24	25-28	29-30	31-32	33-34	35-36	37-38	39-D	0-1	1-2	3-8	9+
106							11.2					
111	7.8	15.9	7.9			16.1	7.3					11.1
113				21.7	25.8					4.5		
118				1.9								
124					5.5				5.2			
127	2.5	11.2										
b) FOOT												
106							10.6					
111	1.9	1.6	1.8			3.4		1.4				3.7
113				17.2	8.5					2.5		
c) FOREARM												
92						3.1						
106						2.0	2.5					
111	1.5	1.7				3.2		2.0				2.6
113				1.4	2.5							3.3
123	2.9	2.0				2.5						
124					1.6	1.6						
127	1.0	1.0										
d) CALF												
127	1.0	2.1										

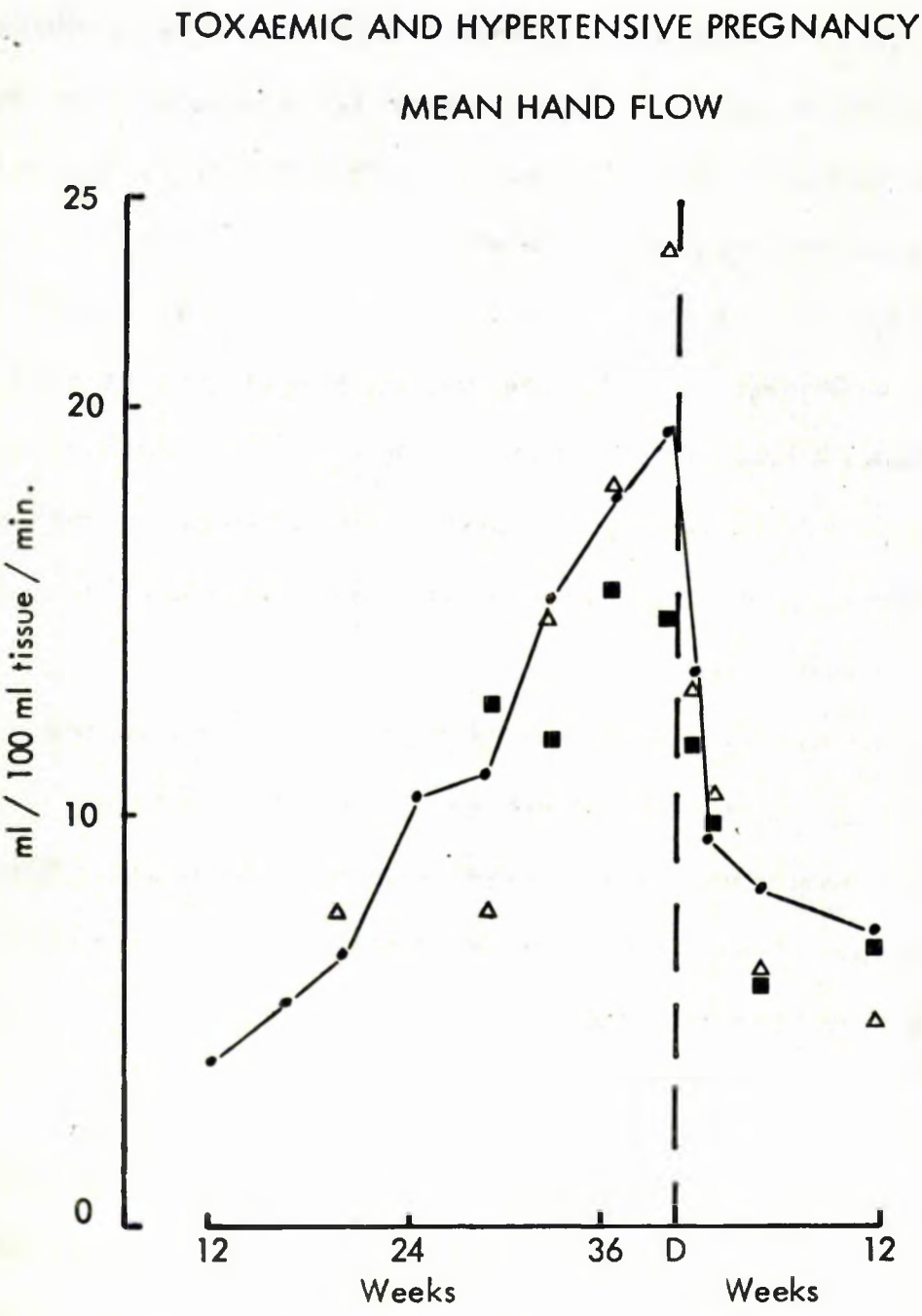


Fig. 21. Mean hand flow in women with severe toxaemia (■) and essential hypertension (△) in pregnancy and the puerperium. The values for normotensive women (•) are given for comparison.

HAND

A total of 165 recordings were made in 36 patients (Fig. 21). Hand blood flow increased in hypertensive and toxaemic patients as in normotensive women. The wide scatter of individual values both in normotensive and hypertensive pregnancy precludes interpretation of minor variations in mean flow. In the patients with essential hypertension who developed toxaemia (at varying stages of pregnancy) the onset of toxaemia was not associated with any reduction in flow. During the first week of the puerperium, hand flow remained elevated in hypertensive as in normotensive women, non-pregnant levels being regained only after several weeks.

The six subjects who had hand blood flow measured while on hypotensive drugs (Table XXI) were on a variety of agents: reserpine, guanethidine, methyl-dopa ("Aldomet") and 10-methoxy deserpidine ("Decaserpyl"). The numbers are too small to derive mean values for patients on a particular drug.

FOOT

Of the group of hypertensive subjects, 27 were studied on 96 occasions. In most, there was some increase in foot blood flow in late pregnancy. As shown in Fig. 22, the mean values in patients with toxaemia are lower than those obtained in normotensive women. In the group studied between 35 and 38 weeks of pregnancy, when the difference is greatest and the numbers largest, a t-test showed that the difference between the mean values was not significant ($t = 1.62$, $p > 0.1$).

TOXAEMIC AND HYPERTENSIVE PREGNANCY

MEAN FOOT FLOW

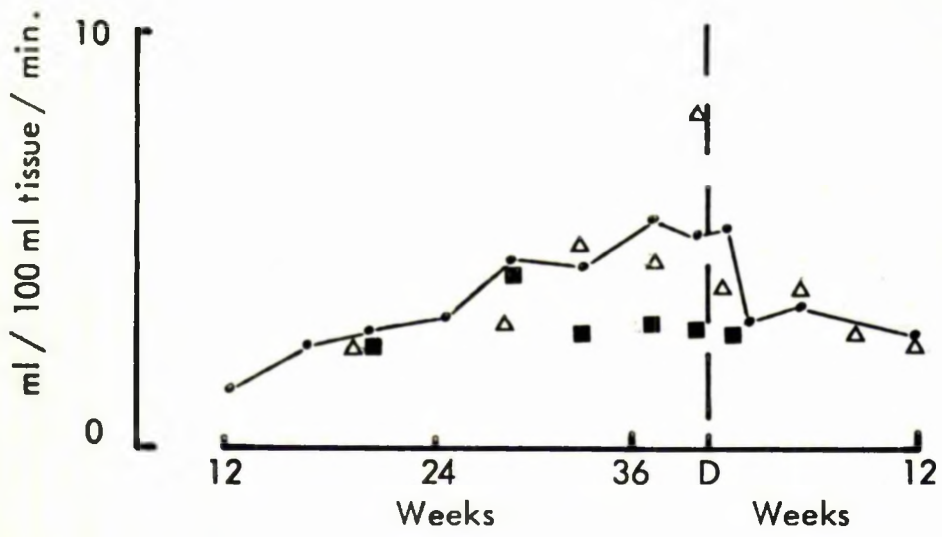


Fig. 22. Mean foot flow in women with severe toxaemia (■) and essential hypertension (△) in pregnancy and the puerperium. The values for normotensive women (•) are given for comparison.

Most of the studies in toxaemia were in women in the 'severe' category, in some of whom, oedema is a prominent feature. If the volume of the segment increased and the actual inflow remained the same, expression of the rate in ml/100 ml tissue would show an erroneously low value. Since the co-relation between clinical oedema and volume change is not considered to be close (Theobald and Lundberg 1963) no attempt was made to compensate for this factor but it could tend to lower the mean foot flow for the group.

FOREARM

Measurements were made on a total of 53 women on 233 occasions (Fig. 23). Forearm blood flow showed no change in any of the hypertensive states studied, the mean value being similar throughout to that of normotensive women in pregnancy.

CALF

Similarly, calf blood flow recorded on 58 occasions in 14 subjects showed mean values close to those found in normotensive women (Fig. 24).

TWINS WITH TOXAEMIA

In the two patients studied, there was no consistent evidence of a reduction in blood flow in the segments studied (Table XX).

PATIENTS ON HYPOTENSIVE DRUGS

The results in Table XXI are those obtained in all limbs in

MEAN FOREARM FLOW

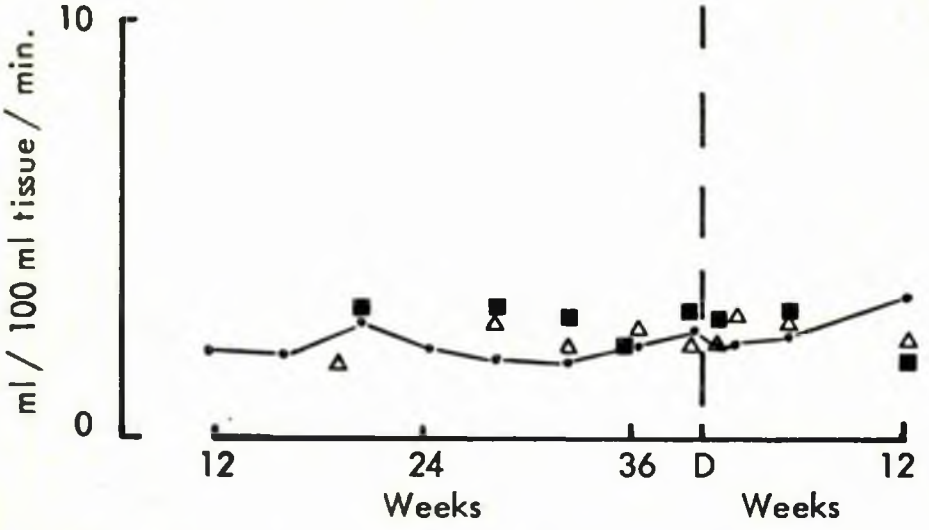


Fig. 23. Mean forearm flow in women with severe toxaemia (■) and essential hypertension (△).

MEAN CALF FLOW

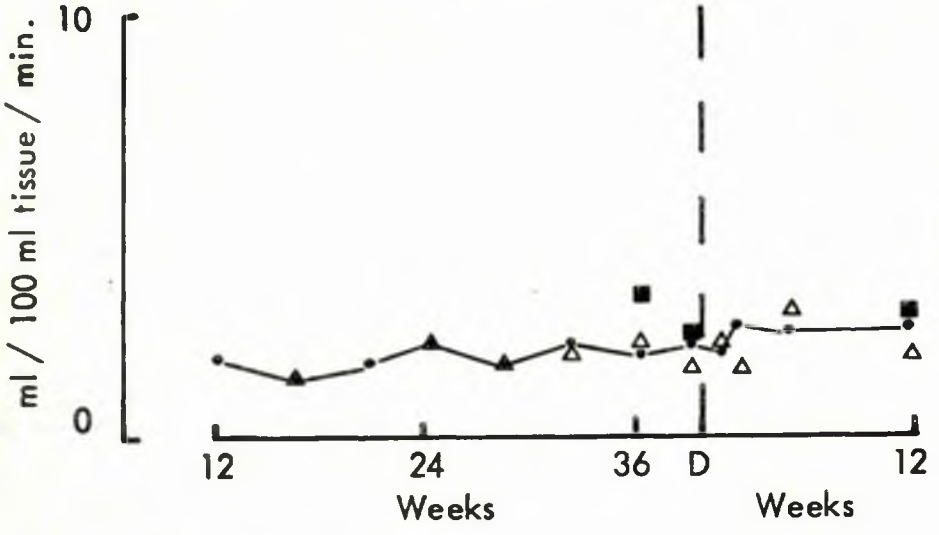


Fig. 24. Mean calf flow in women with severe toxaemia (■) and essential hypertension (△).

patients during, or within two weeks of hypotensive therapy. Mean values have not been derived but the individual results are similar to those obtained on patients not on hypotensive drugs.

TABLE XXII - PULSE RATE - NORMOTENSIVE AND HYPERTENSIVE PREGNANCY

GROUP		WEEKS OF PREGNANCY								WEEKS AFTER DELIVERY			
		Under 14	15-18	19-22	23-26	27-30	31-34	35-38	39-D	D-1	1-2	3-8	9+
NORMO-TENSIVE SINGLE PREGNANCY	MEAN	83	82	82	86	86	86	85	84	76	75	73	73
	RANGE	70-100	65-94	72-96	68-100	73-96	67-116	58-120	66-109	56-109	64-85	55-97	52-81
		(17)	(11)	(15)	(22)	(17)	(16)	(54)	(26)	(63)	(6)	(28)	(15)
NORMO-TENSIVE TWIN PREGNANCY	MEAN	-	-	-	-	92	93	80	82	83	76	-	68
	RANGE	-	-	-	-	90-96	72-112	57-100	65-96	64-114	60-88	-	64-72
						(3)	(12)	(16)	(4)	(9)	(3)		(3)
MILD TOXAEMIA	MEAN	72	84	83	83	81	82	81	79	79	77	70	71
	RANGE						66-100	68-96	68-96	68-92	64-89	60-74	65-75
		(1)	(1)	(2)	(1)	(2)	(5)	(10)	(7)	(7)	(6)	(4)	(3)
SEVERE TOXAEMIA	MEAN	83	76	77	81	88	79	78	76	76	77	76	77
	RANGE					74-100	64-99	64-104		64-92	72-86	63-88	71-88
		(1)	(1)	(1)	(1)	(6)	(6)	(14)	(2)	(13)	(3)	(3)	(9)
ESSENTIAL HYPER-TENSION	MEAN	-	-	76	77	77	88	80	78	78	68	76	71
	RANGE	-	-	65-84	72-83	60-97	75-100	70-95	68-91	58-86	50-84	66-84	67-76
				(3)	(3)	(5)	(13)	(15)	(4)	(7)	(4)	(3)	(6)

NUMBER AVERAGED IN PARENTHESIS

PULSE RATE

The mean pulse rates and range of values found in the different hypertensive groups are shown in Table XXII in relation to those obtained in single and twin pregnancy. The mean values are similar.

SUMMARY OF RESULTS ON LIMB BLOOD FLOW IN HYPERTENSIVE PREGNANCY

Compared with normotensive women at the same stage of gestation, there is no reduction in limb blood flow in women with established hypertension or in those in whom toxaemia develops.

NORMOTENSIVE AND HYPERTENSIVE PREGNANCY

MEAN FOREARM PERIPHERAL RESISTANCE

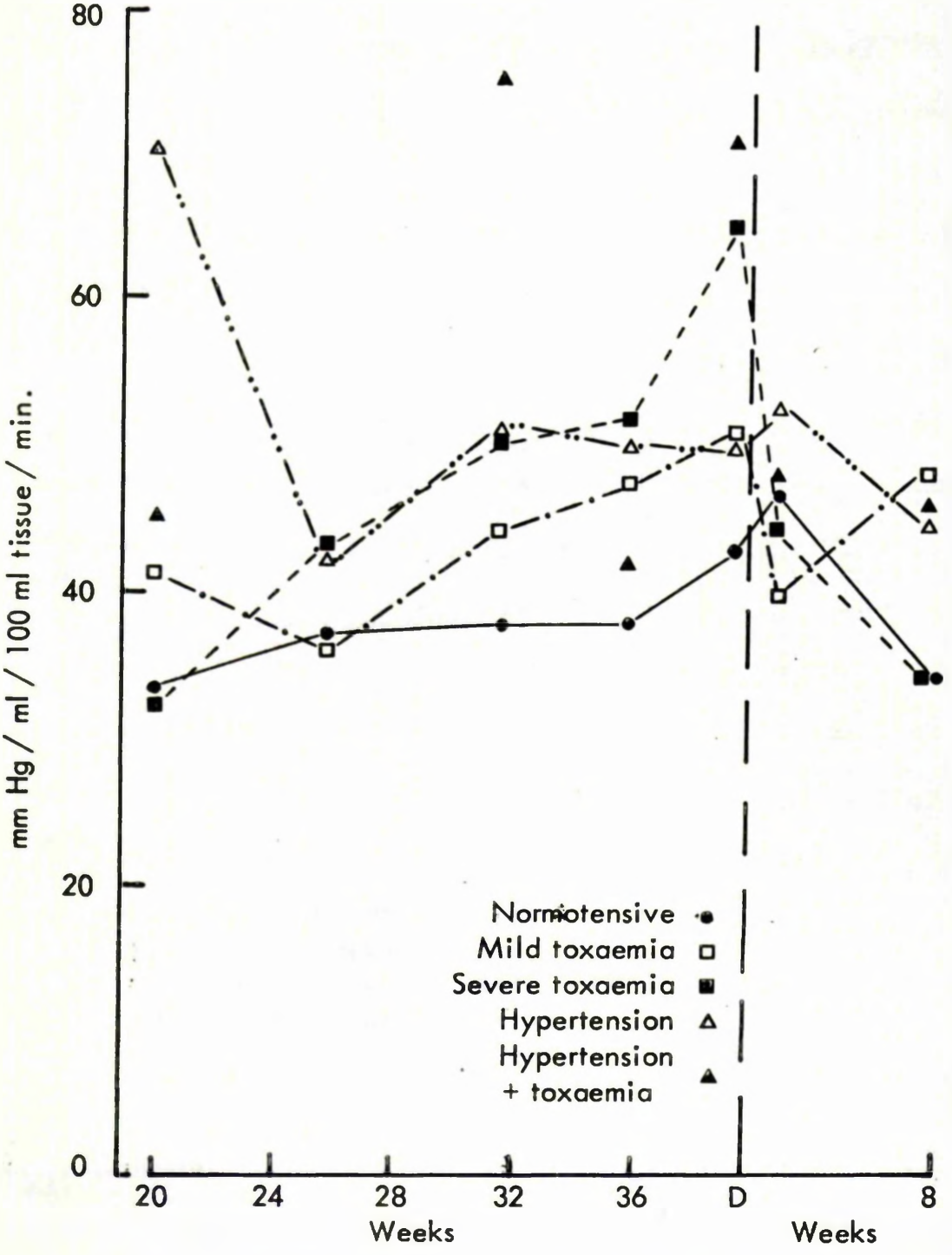


Fig. 25. Forearm peripheral resistance in the different diagnostic groups in pregnancy and after delivery. The rise was greatest in the groups whose blood pressure increased.

RELATIONSHIP OF BLOOD PRESSURE TO FOREARM BLOOD FLOW - PERIPHERAL RESISTANCE

Within the hypertensive states described, there was considerable variation in the blood pressure level for any particular duration of pregnancy. Also, in some of the subjects studied, the blood pressure was not elevated at the time of recording the limb flow measurements. To clarify the relationship, co-relation of forearm flow with the blood pressure recording at the time of measurement has been made in the main groups of subjects studied, thus providing an index of peripheral resistance. This has been derived by dividing the mean blood pressure (diastolic plus 1/3 of the pulse pressure) by the average forearm flow for each occasion. This gives an arbitrary unit expressed in mm Hg/ml/100 ml tissue/minute.

The results obtained in 10 normotensive women (Table XXIII), 14 with mild and 13 with severe toxaemia (Table XXIV) and 15 with essential hypertension plus 4 with hypertension and superimposed toxaemia (Table XXV) can be compared. Fig. 25 illustrates the mean values for each diagnostic group during pregnancy and the puerperium.

RESULTS

In the normotensive women, there is an increase in the peripheral resistance calculated in late pregnancy and the early puerperium. This results from a slight increase in diastolic blood pressure in late pregnancy although the highest readings were only 120/80 and 110/85. This increase in peripheral resistance, from 37.5 units at

TABLE XXIII - FOREARM PERIPHERAL RESISTANCE

NORMOTENSIVE SINGLE PREGNANCY

mm Hg/ml/100 ml tissue/min

Patient Number	WEEKS OF PREGNANCY								WEEKS AFTER DELIVERY			
	Under 24	25-28	29-30	31-32	33-34	35-36	37-38	39-D	0-1	1-2	3-8	9+
18	30*	25		36		46			35	47	51	
21						43	52		53	46	42	
22						28		39	25		19	
26	53	53	58	54								
37	26	27			44	37		58			41	
40						20	19	32	49	30	18	
48	25*	21		30		35		40	40		25	
49				40		49		36*	61		35	
51						47	37	58	36			
52	42		37	29	29				47		44	
MEAN	32.6	36.8		37.4		37.5		42.7	46.9		34.4	

* Average of more than one occasion.

TABLE XXIV - FOREARM PERIPHERAL RESISTANCE

TOXAEMIA OF PREGNANCY

mm Hg/ml/100 ml tissue/min

Patient Number	WEEKS OF PREGNANCY							WEEKS AFTER DELIVERY			
	Under 24	25-28	29-30	31-32	33-34	35-36	37-38	39-D	0-1	1-2	3-8	9+
MILD												
76							38		28	21		
77			26	40		35	36		28			
78								36	47			
79						67		60		59	62	
80								65				
81							28		37			
82	37					40						
83					45		64			45		
84							40			47		
85							42				50	
87						19		50	29			53
88					60		82	49	56		36	40
89			45	38			77		48	32	47	54
90	45*	37		37			53	50	39		45	
MEAN	41	36.0		44.0		47.8		51.7	39.0	40.1	48.0	49.0
SEVERE												
91		53	36	42		33		31	47			
92									39			
93				21					23	27		32
94						53			44			
96						48	33		49			
97								45	75			52
99			56		49	61*			51			
101			17							64	26	30
102						54	75		40			
103						52	51		51			
104								118	59			38
105	32*	38	58	95						31		29
106										24	40	27
MEAN	32.0	43.0		50.2		52.1		64.7	47.8	36.5	33.0	34.7

* Average of more than one occasion.

TABLE XXV - FOREARM PERIPHERAL RESISTANCE

ESSENTIAL HYPERTENSION

mm Hg/ml/100 ml tissue/min

ESSENTIAL HYPERTENSION Patient Number	WEEKS OF PREGNANCY Under 24	25-28	29-30	31-32	33-34	35-36	37-38	39-D	WEEKS AFTER DELIVERY 0-1	1-2	3-8	9+
107						73	89		53			
108	79		55		72		54	62				
109					49	29						
110								30				
112	62	46		39	57	40	77		100		50	
113			55								67	
114				49		62	53	65	41			
115		54			47		28*		72			59
116		31	36		63			51	55		38	
118				33*								
119				57		41	27		42			
120							35			34		29
121								54		49		43
122		17		52	38		64	39	51		42	49
123				69			48			31		26
MEAN	70.0	42.0		50.6		49.9		50.0	52.8		44.8	
ESSENTIAL HYPERTENSION + TOXAEMIA												
124			85	109					64		43	
125										50*		
126	43*		56	67	33*					41	51	47
127	51		140*	70*	147	42		71		38	44	
MEAN	45.3	105.2		75.6					48.6		46.2	

* Average of more than one occasion.

35 - 38 weeks of gestation to 42.7 units at 39 weeks to delivery was associated with a mean change in blood pressure of 109/67 to 109/76. In eight of these women in whom measurements were made a month apart in late pregnancy, comparison of the mean values shows a significant increase in forearm peripheral resistance ($t = 3.154$, $P < 0.02$). The increase was sustained during the first week of the puerperium but by six weeks after delivery a level of 34.4 units, similar to that recorded before 38 weeks gestation, had been regained.

In mild toxaemia, there was a rise in resistance from 30 weeks onwards compared with normotensive women. After the first week of the puerperium peripheral resistance was still raised in the women who had had mild toxaemia.

In severe toxaemia, the mean value was elevated from 26 weeks on when the earliest rise in blood pressure occurred. In the one patient studied on several occasions before the third trimester the mean level was 32 units which was similar to that obtained in normotensive women. There was a sharp rise with the onset of toxaemia at 29 weeks. The increase in the mean value for the group as pregnancy progressed was sustained in the early puerperium. After the immediate puerperium the mean level was the same as that in post-natal normotensive women.

In essential hypertension, peripheral resistance was increased throughout pregnancy compared to normotensive women at the corresponding gestation. The elevation was sustained during and beyond the immediate puerperium.

The mean level of peripheral resistance in the women with essential hypertension and superimposed toxaemia in late pregnancy was greater than in the other hypertensive states. After delivery the values were close to those obtained in women with essential hypertension.

SUMMARY OF ANALYSIS OF FOREARM PERIPHERAL RESISTANCE

There is an increase in peripheral resistance in hypertensive and toxaemic women compared with normotensive women at the corresponding stage of gestation. Several weeks after delivery the mean levels are higher in women who had essential hypertension and mild toxaemia compared with the women who remained normotensive or who developed severe toxaemia.

DISCUSSION OF RESULTS OF LIMB BLOOD FLOW STUDY IN HYPERTENSIVE PREGNANCY

These results show that, compared with normotensive women, there is no reduction in limb flow during pregnancy in women with established hypertension or in those in whom toxaemia develops. Thus, a generalised reduction in flow which involves the extremities, is not associated with hypertensive pregnancy and is not apparently fundamental to the rise in blood pressure.

ROLE OF THE VASCULAR SYSTEM IN HYPERTENSIVE PREGNANCY

Generalised vasospasm, with resulting ischaemia, has long been considered to be an essential feature of the vascular disorder underlying toxaemia of pregnancy (Falkiner 1950, Dieckmann 1952, Mendelson 1960, Taschi 1961, Assali, Holm and Parker 1964, Finnerty 1964, 1966, Chesley 1966). The evidence for this repeated statement has been the presence of placental infarcts and the prominence of vascular lesions in individual organs, notably kidney, liver, brain, adrenal glands and spleen, by biopsy or from post-mortem specimens (Sheehan 1950, M^{c}Kay, Merrill, Weiner, Hertig and Reid 1953, M^{c}Cartney 1964). The main changes include visceral haemorrhages, necrosis and infarction of tissue with thrombosis of vessels. Biopsies of the placental bed have shown pathological changes in toxaemia (Dixon and Robertson 1958, Brosens 1963, 1964) but changes in blood flow cannot be inferred from pathological findings alone. M^{c}Kay and his colleagues (1953) consider that intravascular deposition of fibrin may be the fundamental pathological event rather than vasospasm.

REGIONAL BLOOD FLOW IN HYPERTENSIVE PREGNANCY

Available studies of regional distribution of flow have not provided unequivocal evidence that generalised vasoconstriction is responsible for the rise in blood pressure. Thus, although estimation of uterine blood flow by nitrous oxide (Assali, Douglas, Baird and Nicolson 1953) and by radio-active clearance studies (Morris, Osborn and Payling-Wright 1955) have shown a reduction in women with toxaemia compared with normal pregnancy, hepatic (Munnell and Taylor 1947) and cerebral blood flow (McCall 1949) have not been found to be decreased. Spasm of the retinal arterioles has been claimed in toxaemia (Landesman 1955, Finnerty, Foote, Massaro, Tuckman Buchholz and Ryan 1960, Tacchi 1961) but a reduction in arterielar calibre has also been described in normal pregnancy near term (Landesman 1955). There is, in any case, considerable divergence of opinion concerning the constancy of changes in retinal vessel calibre in toxaemia. Thus, Pickering (1950) stated "I have observed the fundus oculi carefully in several cases of pre-eclamptic toxaemia and have never seen a localised constriction of a retinal artery which disappeared after the blood pressure returned to normal. My ophthalmological friends who have looked at many cases of pregnancy toxaemia also used to tell me that they have never seen it". Pollak and Nettles (1960) consider examination of the retinae to be one of the most useful indicators of the severity of toxaemia while Landesman (1955) stresses that the accuracy of observations is increased if there is a single observer.

The findings concerning renal blood flow in toxaemia are not entirely clear and are complicated by the changes occurring in normal pregnancy. There is considerable evidence of a reduction in glomerular filtration rate in toxaemia (Assali, Kaplan, Formon and Douglass 1953, de Alvarez and Richards 1954, Chesley 1961). Using electron microscopy, a specific lesion of the renal glomeruli which might well account for a reduction in the glomerular filtration rate has been recognised (Pollak and Nettles 1960, Altchek 1961). However, changes in the small renal arteries and arterioles are not consistent and the tubular changes are not specific. Thus, these changes cannot be interpreted in terms of renal blood flow, measurements of which have not been consistent. Bucht and Werkö (1953), Assali and his colleagues (1953) and Chesley (1961) all reported a reduction in renal blood flow and Levitt (1957) only a very slight decrease, while de Alvarez and Richards (1954) found a comparative increase in severe toxaemia.

From these various studies discussed, it is clear that, at the very least, the effects of toxaemia on the vascular system are not equally distributed. One difficulty in the interpretation of studies of toxaemia is that of the diagnosis, which may have to be retrospective. In recent years, the presence of a specific renal lesion has been considered to be the hallmark of the diagnosis of toxaemia of pregnancy but investigation, by renal biopsy, of a large series of subjects with acute hypertension in late pregnancy, clinically 'toxaemic', showed that only 30 per cent had the specific renal lesion. Many others had

histological evidence of chronic renal disease (M°Cartney 1964).

In patients considered to have essential hypertension rather than toxaemia in pregnancy, studies of regional blood flow are few and conflicting. Renal plasma flow has been reported to be low when compared with normal pregnancy (de Alvarez and Richards 1954) while Chesley (1963) found it to be close to normal for the stage of gestation except in a few patients with severe disease where it was reduced. While there are histological changes in the placental bed in essential hypertension (Dixon and Robertson 1961, Brosens 1963) and chorio-decidual clearance has been found to be reduced (Dixon, McClure Browne and Davey 1963), studies of myometrial clearance have not been clear-cut (Morris et al. 1955, Dixon et al. 1963).

Burt (1950a) claimed an increase in forearm blood flow in both toxaemia and hypertension but only a single recording in pregnancy was made in seven and five patients respectively. Furthermore, my analysis of her data does not support the claim of an increased forearm flow in either toxaemia ($t = 1.046$, $P > 0.3$) or hypertension ($t = 1.104$, $P > 0.2$) compared with her own results in normotensive women. Spets (1965) reported a decreased forearm flow in toxaemia compared with normotensive pregnancy but in view of the differences in technique discussed in the previous system, comparison between his and the present series is difficult. Using a calorimetric method of estimation, Mendlowitz, Altshek and Naftchi (1958) found the digital blood flow to be similar in normotensive and hypertensive women in the third

trimester of pregnancy.

Therefore, with the possible exception of the kidneys and uterus, no study of a regional vascular bed in hypertensive pregnancy has shown a reduction in blood flow. The present investigation extends this finding to skin and skeletal muscle.

PERIPHERAL BLOOD FLOW IN NON-PREGNANT HYPERTENSIVE CONDITIONS

The finding, in the present study, that limb blood flow is unchanged (for the stage of gestation) despite an increase in blood pressure may be compared with previous studies in hypertensive non-pregnant subjects.

Although Abramson and Fierst (1942) reported a slight increase in forearm blood flow in hypertensive compared with normotensive subjects, other workers (Pickering 1936, Prinzmetal and Wilson 1936, Doyle, Fraser and Marshall 1959) have found no difference, and in the hand mean flow was unchanged in a group of hypertensive compared with normotensive subjects (Pickering 1936, Duff 1956). However, when Duff subdivided his results according to the severity of hypertension, he found an increase in hand flow in the milder of his hypertensive subjects (with a diastolic blood pressure below 130 mm Hg) and a decrease in the most severe group (with a diastolic level above 160 mm Hg). In the present series, the maximum blood pressure recorded at the time of study was 190/120 and it is therefore not possible to state whether there is a lower than normal hand blood flow in late pregnancy in very severe degrees of hypertension. In acute nephritis, Pickering (1955) found

that hand blood flow was in the upper range of normal, the level falling slightly as the blood pressure returned to normal.

PERIPHERAL RESISTANCE IN HYPERTENSIVE PREGNANCY

Bucht and Werkö (1953) and Assali, Holm and Parker (1964) have found no alteration in cardiac output in patients with toxaemia compared with normal pregnancy despite a lowering of renal blood flow and conclude that in toxaemia, the resistance in the renal vessels is greater than in other vascular beds, a suggestion compatible with the results of the present study. The finding that in hypertensive pregnancy, despite the greater perfusion pressure, limb blood flow was similar to that found in normal pregnancy suggests an increase in peripheral resistance in hypertensive pregnancy. Analysis of individual results in the forearm indicates that this is so and that the increase is greater in the more severely hypertensive subjects. Similar conclusions have been reached in respect of digital (Mendlowits, Altchek and Naftchi 1958) and cerebral (M°Call 1947) vascular resistance in toxaemia. The slight rise found in diastolic blood pressure in normal pregnancy towards term agrees with previous studies of blood pressure in pregnancy (Hare and Karn 1929, Henry 1936, Burwell 1938). This rise, unassociated with an increase in forearm blood flow, implies an increase in peripheral vascular resistance even in these subjects considered to be normotensive throughout their pregnancy.

This slight increase in peripheral resistance in normal subjects near term and greater increase in hypertensive subjects in pregnancy is

an expression of the pressure/flow relationship in a regional vascular bed. It must be associated with a change in the calibre of blood vessels to maintain the flow constant despite a change in perfusion pressure. Vasoconstriction or vasospasm are not, however, implied; these terms can possess meaning only if applied to a reduction in blood flow.

Peripheral resistance after the first week of the puerperium was greater in women with mild toxaemia than in those with severe toxaemia. It has been suggested (Adams and MacGillivray 1961) that women with only a slight rise in blood pressure and in whom pregnancy tends to pursue a benign course constitute a different group from those with severe toxaemia accompanied by proteinuria and may be suffering from latent hypertension revealed by the pregnancy. These authors found that women with only a slight elevation of blood pressure in late pregnancy tended to have a higher blood pressure when examined fifteen years later, compared with a group showing more severe signs of toxaemia where the blood pressure level corresponded more closely to that of women of the same age who had not had toxaemia. The present finding of a higher peripheral resistance in the weeks after delivery in patients with mild toxaemia compared with severe toxaemia or normotensive pregnancy may be considered to provide added support for this concept.

The findings that vasodilatation is unaltered in the hand and that forearm blood flow is not reduced in hypertensive pregnancy, make

it unlikely that a generally circulating humoral vaso-constrictor substance is responsible for toxaemia of pregnancy. The possibility of a constrictor agent with localised regional effects has not, however, been excluded.

Although increased sensitivity to constrictor agents has frequently been claimed in toxaemia of pregnancy (Browne 1943, Raab 1957, Browne 1958, Roszkowski and Kuszynska-Sicinska 1964, Chesley 1965) the conclusion has been based on studies of changes in systemic pressure. Assali, Vergon, Tada and Garber (1952) postulate a humoral mechanism maintaining blood pressure in toxaemia since the reduction of the blood pressure to autonomic blockade, either by spinal anaesthesia or by tetra-ethyl ammonium chloride (TEAC) was found by them to be less in women with toxaemia than in normotensive women or those with essential hypertension in pregnancy. However, the pooling of blood which results from autonomic blockade complicates the interpretation of this manoeuvre in pregnancy and the reaction has not been found to be sufficiently consistent to differentiate hypertensive states in pregnancy (Chesley and Valenti 1958). Direct evidence of increased constrictor response in specific vascular beds in hypertensive pregnancy is lacking.

It is clear, therefore, that further study of regional vascular beds in pregnancy is required, particularly their response to standard constrictor or dilator stimuli. Comparison of baroreceptor and chemoreceptor reflex activity in hypertensive and normotensive subjects in pregnancy would also provide information concerning the regulation of blood pressure in toxaemia.

SUMMARY AND CONCLUSIONS OF LIMB BLOOD FLOW STUDY IN HYPERTENSIVE PREGNANCY

1. Hand and foot blood flow increase in pregnancy while forearm and calf blood flow remain unchanged in pregnant women who develop toxaemia and in those with hypertension before and during pregnancy. The levels of limb blood flow are similar to those found in normotensive women at the same stage of pregnancy or the puerperium.

2. In normotensive women near term the maintenance of a constant forearm flow despite a slight increase in perfusion pressure is associated with an increase in peripheral resistance. In hypertensive pregnancy, the greater increase in perfusion pressure is associated with a correspondingly greater degree of peripheral resistance. The nature of this increase in peripheral resistance in hypertensive pregnancy is not known.

3. Comparison of these findings with those found in other regional vascular beds in hypertensive pregnancy and with those obtained in non-pregnant hypertensive states is discussed.

4. If the rise in blood pressure in hypertensive pregnancy is associated with a reduction of blood flow to any region, this must be in vascular beds other than skin and skeletal muscle. It is unlikely, therefore, that a generally circulating vasoconstrictor agent is involved.

PRESENT STUDY - SECTION II

ARTERIOLAR DISTENSIBILITY IN RESPONSE TO VASODILATATION IN NORMOTENSIVE AND HYPERTENSIVE PREGNANCY

ARTERIOLAR DISTENSIBILITY IN HYPERTENSIVE AND NORMOTENSIVE PREGNANCY

The finding, detailed in the previous section, that the peripheral resistance in the limbs increases in normal pregnancy towards term and increases to a greater extent in hypertensive pregnancy prompted further studies. The response of a regional vascular bed to a vasodilator stimulus was investigated by comparing the ability of the forearm vessels to dilate at different stages of pregnancy in both normotensive and hypertensive women.

ROLE OF PERIPHERAL RESISTANCE IN NON-PREGNANT HYPERTENSION

In arterial hypertension in non-pregnant subjects, an increase in peripheral resistance constitutes one of the important established facts (Prinzmetal and Wilson 1936, Pickering 1955, Conway 1963a). However, the cause of this increase in peripheral resistance is unknown and Conway (1963a) has deplored the scant attention paid to the function of peripheral blood vessels. This neglect is even more true of hypertension in pregnancy.

Changes in the calibre of the small vessels, comprising arterioles, metarterioles and capillaries are the main determinant of peripheral resistance, accounting for about 80% of its variation (Wiggers 1952). In essential hypertension, the increase in pressure gradient occurs only beyond the small arteries and is thought to be located almost entirely in the pre-capillary arterioles (Weiss and Ellis 1929, Oppenheimer and Prinzmetal 1937).

In hypertensive states, these vessels may be structurally normal but maintained in a constricted state by some humoral or nervous mechanism or there may be a change in their physical characteristics. The older concept that increased resistance is associated with a rigid sclerotic narrowing of the small resistance vessels (Brown and Alexander 1935) has not been substantiated by studies, since it has been shown that the vessels of hypertensive subjects are distensible (Prinzmetal and Wilson 1936) and generally dilate readily to dilator agents (Folkow, Grimby and Thulesius 1958). The activity of the smooth muscle in these vessels is readily affected by humoral and neurogenic stimuli and it has been assumed that there is an increased level of vasoconstrictor tone in hypertension. This view prevailed widely and led to the inception of sympathectomy for hypertension (Rowntree and Adson 1925, Brown 1934), but the long-term effect of this procedure has proved to be disappointing (discussed by Pickering 1955). More recently, in reference to essential hypertension, Pickering (1961) has stated: "Over-action of the sympathetic nerves, of the adrenal medulla, of the adrenal cortex, of the pituitary and of the renin-angiotensin system have never been displayed". Conway (1963b) supports the finding that there is no increase in vasoconstrictor tone in essential hypertension.

Folkow and his co-workers (1958) have adduced considerable evidence that the resistance vessels can exert a large degree of auto-regulation of vascular beds, and consider that this basal vascular tone is a truly myogenic activity. An example of auto-regulation of regional

vascular beds can be found in co-aretation of the aorta, where there is no consistent change in upper and lower limb blood flow compared with normal subjects despite the considerable difference in the mean blood pressure between upper and lower limbs (Pickering 1936, Wakim, Slaughter and Claggett 1948). This increase in resistance in the forearm compared with the calf blood vessels has been shown to persist with local vasodilatation (Patterson, Shepherd and Whelan 1957).

The ability of forearm vessels of hypertensive subjects to dilate in response to a vasodilator stimulus was shown to be at least as great as that in normotensive subjects (Prinzmetal and Wilson 1936, Pickering 1936). However, at the time of these studies, the necessity of occluding venous return from the hand while measuring forearm flow was not appreciated and the findings cannot be interpreted quantitatively. Wilkins and Richns (1941), using a technically satisfactory method, found that the forearm vessels in hypertensive subjects dilated at least to the same extent as in normal vessels and in some subjects found that the maximum flow obtained was greater, to a degree commensurate with the increase in blood pressure. More recently this aspect of arteriolar function has been re-investigated (Folkow et al. 1958, Conway 1963b) and both groups show that even when maximal or near maximal vasodilatation is produced, there is evidence of increased resistance to flow in hypertensive compared with normotensive subjects. Folkow and his co-workers have further suggested that if an increased wall to lumen ratio in the resistance vessels occurs in hypertensive states the

increased wall mass per se will result in a higher flow resistance in hypertension for a given level of smooth muscle tone. Moreover, an increase in "intrinsic" vascular tone may occur as a result of an increase in pressure by strictly local influences on resistance vessels without implying specific vasoconstrictor agents or increased smooth muscle sensitivity.

These studies were carried out in patients of both sexes with long-standing hypertension due to a variety of causes and with some subjects on prolonged anti-hypertensive therapy. Thus the findings are not necessarily applicable to hypertension in pregnancy which is often of recent or acute onset and, on average, involves younger subjects.

PRESENT STUDY OF ARTERIOLAR DISTENSIBILITY

The present study was carried out to establish whether the increased resistance to blood flow found in normotensive pregnancy near term, and to a greater extent in hypertensive pregnancy, was maintained or abolished during vasodilatation.

METHOD AND SUBJECT

The stimulus used was a ten minute period of arterial occlusion with brief exercise of the forearm muscles early in the period of occlusion. This procedure is followed by a period of reactive and exercise hyperaemia which is independent of vasomotor control (Lewis and Grant 1925 , Dornhorst 1963).

A total of 296 studies was made in 70 patients. Clinical classification into normotensive and hypertensive subjects was made according to the criteriae previously described (p. 88). An additional group who had a history of toxaemia in a previous pregnancy but who did not develop toxaemia (a rise of blood pressure to 140/90 or over on two separate occasions in the last trimester of pregnancy) was also studied. Most of the patients are also included in the previous section. In the relevant table in the Appendix containing clinical details, the women of the present study are indicated.

The patients comprised the following groups:-

A) 16 normotensive women - single pregnancy - Table A

B) 10 normotensive women - multiple pregnancy - Table B

C) 39 hypertensive women -

(i) 13 with mild toxaemia - Table E

(ii) 13 with severe toxaemia - Table F

(iii) 9 with essential hypertension - Table G

(iv) 2 with essential hypertension and superimposed toxaemia - Table H

(v) 2 with twins and toxaemia - Table I

D) 5 normotensive women with previous toxaemia - Table J

Forearm blood flow in these women was carried out as previously described, the plethysmograph water temperature being maintained at 34 ± 1°C throughout the procedure and the conditions being standardised as before. The same forearm (usually the left) was studied in each patient on subsequent occasions, the volume of the segment being measured

on each occasion. After the apparatus was assembled and any necessary adjustments made, the forearm flow was recorded at half minute intervals for at least five minutes after a steady flow was obtained. The average of the readings obtained was taken as the resting forearm blood flow. Arterial occlusion to the forearm was then applied by instantaneous inflation of the cuff around the upper arm to a pressure of at least 100 mm Hg above the systolic blood pressure. A check was made that the arterial occlusion was efficient by observing that the water level in the plethysmograph did not rise. After the first two minutes, the patient gripped a sphygmomanometer bulb and squeezed it firmly ten times against resistance.

Following ten minutes of occlusion the pressure in the upper cuff was released suddenly and then immediately re-applied to provide venous occlusion, the first reading being taken within five seconds of release of occlusion. During the first minute the collecting pressure used was 40 mm Hg since Patterson and Whelan (1955) have shown that with very high rates of flow, as occur with reactive hyperaemia, the pressure gradient along the main arteries is considerable and a higher collecting pressure may interfere with arterial inflow. Thereafter, the usual collecting pressure of approximately 10 mm Hg below the diastolic blood pressure was used. The maximal flow recording was usually obtained about fifteen seconds after release of arterial occlusion. During the first minute, therefore, blood flow recordings were taken every five to ten seconds. Thereafter, flows were measured every quarter

minute until a value judged to be close to the resting value was obtained or for at least ten minutes. In a few patients where the level was still clearly elevated compared with the control flow and where there was no sign of restlessness, recordings were continued for a further few minutes. Wrist arterial occlusion was maintained throughout the procedure. Blood pressure was measured by auscultation in the opposite arm at the beginning and end of the procedure and also during the period of occlusion. The average of the readings was used to obtain the mean blood pressure. Pulse rate was counted from the plethysmographic record.

After occlusion, the drop in arterial pressure in the brachial artery is small and is no greater in hypertensive than in normotensive subjects (Folkow et al. 1958, Conway 1963b). The blood pressure measured in the opposite arm was therefore considered to be valid for the calculation of resistance in the arm under study.

CALCULATION AND PRESENTATION OF RESULTS

Forearm blood flow is expressed throughout in ml/100 ml tissue/ minute. Tables XXVI - XXXIII give the results according to the diagnostic subdivisions. Within each group the findings have been analysed according to the stage of gestation and the mean of the studies made within each period indicated, is given.

Each Table gives the average resting flow and the average peak blood flow during hyperaemia for the different stages of pregnancy and the puerperium.

TABLE XXVI

FOREARM VASODILATATION FOLLOWING ARTERIAL OCCLUSION AND EXERCISE

NORMOTENSIVE SUBJECTS - SINGLE PREGNANCY

Stage of Pregnancy*	MEAN Forearm Blood Flow ø		MEAN Increment Blood Flow				MEAN ø B.P.	MEAN ø Peripheral Resistance	
	Resting	Peak	Peak	After 3 mins	After 10 mins	TOTAL		Resting	Peak
	ml/100 ml tissue/min		ml/100 ml tissue/min			ml/10 mins		mm Hg/ml/100 ml tissue/min	
Under 18 weeks (7)	2.6 (1.5-3.4)	31.2 (22.6-42.0)	28.6	6.2	0.6	66.4	78 (73-93)	32.3 (21-53)	2.78 (1.8-4.0)
19 - 22 (5)	2.8 (1.9-4.0)	29.8 (21.5-30.0)	27.0	7.2	0.3	69.6	80 (73-83)	31.0 (21-42)	2.90 (1.7-3.7)
23 - 26 (8)	2.2 (1.4-3.2)	28.8 (20.8-32.0)	26.6	5.3	0.3	56.5	81 (70-90)	39.6 (25-64)	2.84 (2.6-3.1)
27 - 30 (7)	2.0 (1.0-3.3)	25.6 (12.0-34.6)	23.6	4.3	0.5	52.2	81 (71-99)	48.1 (21-90)	3.97 (2.0-7.5)
31 - 34 (8)	2.1 (1.5-2.6)	30.9 (26.8-34.4)	28.8	5.9	0.7	57.5	81 (73-92)	39.6 (30-53)	2.65 (2.3-3.2)
35 - 38 (10)	2.4 (1.7-3.5)	34.3 (24.4-44.0)	31.9	5.5	1.1	65.2	83 (67-92)	37.4 (19-49)	2.53 (1.5-3.4)
39-Delivery (10)	2.0 (1.6-2.8)	33.6 (25.3-38.4)	31.6	6.2	1.1	67.5	88 (82-93)	45.0 (33-58)	2.72 (2.2-3.3)
Del.-24 hrs. (5)	2.0 (1.4-2.5)	30.0 (22.8-34.6)	28.0	4.0	0.1	53.6	88 (80-100)	46.5 (35-62)	3.07 (2.5-3.6)
2-7 days (5)	2.5 (1.6-3.8)	35.6 (24.8-44.0)	33.1	4.9	0.8	64.3	87 (80-93)	38.2 (24-54)	2.60 (1.8-3.6)
1-2 weeks (3)	2.1 (1.8-2.8)	28.7 (23.6-32.4)	26.6	3.2	0.0	43.1	84 (83-85)	40.7 (30-46)	2.97 (2.6-3.5)
6 weeks + (9)	2.5 (1.6-4.1)	30.3 (25.0-42.5)	27.8	5.6	0.6	67.2	80 (70-83)	36.6 (18-52)	2.67 (1.9-3.2)

* Number of studies at each stage in parenthesis. ø Range of values obtained is given.

TABLE XXVII FOREARM VASODILATATION FOLLOWING ARTERIAL OCCLUSION AND EXERCISE

NORMOTENSIVE SUBJECTS - TWIN PREGNANCY

[1 recording in triplets in brackets]

Stage of Pregnancy*	MEAN Forearm Blood Flow ∮		MEAN Increment Blood Flow				MEAN ∮ B.P.	MEAN Peripheral Resistance ∮	
	Resting	Peak	Peak	After 3 mins	After 10 mins	TOTAL		Resting	Peak
	ml/100 ml tissue/min		ml/100 ml tissue/min			ml/10 mins		mm Hg/ml/100 ml tissue/min	
27-34 weeks (6) [1]	2.8 (2.0-5.1) [3.5]	30.4 (20.5-40.2) [40.0]	27.6 [36.5]	5.4 [3.5]	1.3 [2.7]	67.0 -	82 (71-93)	35.6 (31-42) [26.3]	3.06 (2.1-3.9) [2.30]
35 - 38 (5)	2.6 (1.9-3.8)	35.5 (20.4-37.2)	32.9	4.3	1.4	60.0	91 (83-101)	41.4 (23-65)	2.72 (2.2-4.1)
39-Delivery (5)	2.4 (1.3-4.0)	28.0 (21.6-33.4)	25.6	3.7	1.5	54.4	89 (83-102)	43.2 (21-64)	3.20 (2.8-3.8)
Delivery-2 weeks (5)	2.8 (1.4-4.9)	36.6 (34.0-40.6)	33.8	7.5	1.7	78.2	87 (77-103)	37.4 (19-74)	2.40 (2.3-2.6)

* Number of studies at each stage in parenthesis. ∮ Range of values obtained is given.

TABLE XXVIII FOREARM VASODILATATION FOLLOWING ARTERIAL OCCLUSION AND EXERCISE

HYPERTENSIVE SUBJECTS - MILD TOXAEMIA

Stage of Pregnancy*	MEAN Forearm Blood Flow ♯		MEAN Increment Blood Flow				MEAN ♯ B.P.	MEAN Peripheral Resistance ♯	
	Resting	Peak	Peak	After 3 mins	After 10 mins	TOTAL		Resting	Peak
	ml/100 ml tissue/min		ml/100 ml tissue/min			ml/10 mins		mm Hg/ml/100 ml tissue/min	
Under 30 weeks (6)	2.5 (1.8-3.7)	42.8 (31.0-59.0)	40.3	8.5	1.5	85.9	93 (90-96)	39.2 (26-45)	2.35 (1.6-3.1)
31 - 34 (5)	2.1 (1.5-2.4)	37.5 (27.6-58.0)	35.4	5.2	0.6	60.0	93 (90-98)	45.8 (37-60)	2.68 (1.6-3.4)
35- 38 (10)	2.4 (1.1-4.7)	29.0 (15.0-40.0)	26.6	6.2	1.3	68.5	96 (87-113)	46.7 (18-82)	3.58 (2.2-6.5)
39-Delivery (5)	2.3 (1.8-3.0)	34.5 (21.0-40.2)	32.2	6.4	1.0	69.7	100 (93-108)	46.2 (36-59)	3.06 (2.5-4.6)
Delivery-1 week(6)	2.4 (1.7-3.3)	34.5 (25.2-45.0)	32.6	5.4	0.4	63.2	92 (77-103)	40.0 (27-54)	2.73 (2.0-3.7)
1-2 weeks (5)	2.1 (1.6-3.1)	29.5 (21.2-36.8)	27.4	5.0	0.5	59.2	96 (90-100)	46.6 (32-59)	3.36 (2.7-4.5)
6+ weeks (7)	2.3 (1.4-2.8)	31.0 (26.0-37.2)	28.7	8.1	1.3	74.5	95 (87-103)	44.1 (25-62)	3.14 (2.6-3.7)

* Number of studies at each stage in parenthesis. ♯ Range of values obtained is given.

TABLE XXIX

FOREARM VASODILATATION FOLLOWING ARTERIAL OCCLUSION AND EXERCISE

HYPERTENSIVE SUBJECTS - SEVERE TOXAEMIA

Stage of Pregnancy*	MEAN Forearm Blood Flow ♯		MEAN Increment Blood Flow				MEAN ♯ B.P.	MEAN Peripheral Resistance ♯	
	Resting	Peak	Peak	After 3 mins	After 10 mins	TOTAL		Resting	Peak
	ml/100 ml tissue/min		ml/100 ml tissue/min			ml/10 mins		mm Hg/ml/100 ml tissue/min	
Under 26 weeks (3)	3.1 (2.2-4.4)	30.6 (28.8-40.2)	27.5	13.7	1.1	-	88 (83-97)	31.7 (19-44)	2.70 (2.1-3.5)
27 - 30 (7)	3.0 (1.8-6.9)	32.7 (25.4-37.0)	29.7	8.6	2.2	78.8	106 (92-120)	41.6 (17-58)	3.30 (2.2-4.2)
31 - 34 (6)	2.7 (1.1-5.7)	31.0 (21.0-45.0)	28.3	5.6	1.4	62.9	110 (101-120)	51.3 (21-95)	3.73 (2.7-5.3)
35-38 (10)	2.2 (1.3-3.2)	31.5 (22.2-42.0)	29.3	5.5	1.4	65.3	106 (87-127)	52.2 (33-85)	3.55 (2.3-4.8)
39-Delivery (3)	2.3 (1.0-3.5)	31.4 (27.4-34.8)	29.1	7.1	0.9	63.5	113 (109-118)	64.7 (31-118)	3.63 (3.4-4.0)
Delivery-1 week (9)	2.5 (1.4-5.1)	30.3 (17.2-38.0)	27.8	5.7	0.7	59.1	106 (83-118)	47.4 (23-75)	3.63 (2.9-5.6)
1 - 2 weeks (3)	3.0 (1.7-4.2)	33.9 (22.6-39.8)	30.9	10.5	1.2	89.8	105 (93-115)	40.7 (27-64)	3.37 (2.4-4.8)
6+ weeks (9)	2.8 (2.0-4.1)	27.9 (15.6-39.8)	25.2	8.0	1.0	72.0	94 (83-109)	35.2 (26-54)	3.99 (2.4-6.0)

* Number of studies at each stage in parenthesis.

♯ Range of values obtained is given.

TABLE XIX

FOREARM VASODILATATION FOLLOWING ARTERIAL OCCLUSION AND EXERCISE

HYPERTENSIVE SUBJECTS - ESSENTIAL HYPERTENSION

Stage of Pregnancy*	MEAN Forearm Blood Flow ♯		MEAN Increment Blood Flow				MEAN ♯ B.P.	MEAN Peripheral Resistance ♯	
	Resting	Peak	Peak	After 5 mins	After 10 mins	TOTAL		Resting	Peak
	ml/100 ml tissue/min		ml/100 ml tissue/min			ml/10 mins		mm Hg/ml/100 ml tissue/min	
Under 26 weeks (4)	2.1 (1.2-3.2)	35.3 (21.2-50.0)	33.2	7.5	1.8	79.4	100 (95-105)	54.2 (30-79)	3.10 (2.0-4.5)
27 - 34 (9)	2.0 (1.3-4.5)	31.5 (21.2-44.0)	29.5	4.5	1.1	57.2	105 (93-141)	54.7 (39-72)	3.53 (2.2-5.0)
35 - 38 (10)	2.6 (1.2-4.5)	36.7 (22.1-56.0)	34.1	10.2	1.7	86.5	119 (103-133)	53.2 (27-89)	3.50 (2.1-5.6)
39-Delivery (3)	2.0 (1.9-2.2)	30.6 (25.0-41.3)	28.6	5.8	1.1	60.3	111 (103-117)	55.7 (51-62)	4.27 (2.7-5.5)
Delivery-1 week (4)	2.1 (1.2-2.9)	39.8 (32.2-45.0)	37.7	7.3	1.8	82.5	120 (110-128)	62.5 (42-100)	3.07 (2.4-4.0)
1 - 2 weeks (3)	3.5 (2.3-4.2)	41.7 (34.2-52.0)	38.2	9.8	1.8	97.5	125 (113-141)	37.3 (30-49)	3.07 (2.7-3.6)
6+ weeks (6)	3.4 (2.2-5.3)	34.5 (25.0-45.8)	31.1	7.0	0.9	76.4	129 (110-153)	42.6 (34-84)	3.82 (3.0-5.1)

* Number of studies at each stage in parenthesis.

♯ Range of values obtained is given.

TABLE XXXI FOREARM VASODILATATION FOLLOWING ARTERIAL OCCLUSION AND EXERCISE

HYPERTENSIVE PREGNANCY - ESSENTIAL HYPERTENSION + TOXAEMIA

Stage of Pregnancy*	Forearm Blood Flow		Increment Blood Flow			MEAN B.P.	Peripheral Resistance	
	Resting	Peak	Peak	After 3 mins	After 10 mins		Resting	Peak
	ml/100 ml tissue/min		ml/100 ml tissue/min				mm Hg/ml/100 ml tissue/min	
PATIENT NO. 124								
30 - 32 weeks (2)	1.3	27.8	26.5	2.3	0.1	120	97.0	4.33
† x 34 weeks (1)	1.6	31.2	29.6	2.8	- 0.3	125	78.0	4.00
† D + 4 days (1)	1.9	40.2	38.3	3.7	0.0	122	64.3	3.04
D + 4 weeks (1)	2.6	30.0	37.4	7.6	0.2	113	43.4	3.76
PATIENT NO. 126								
Before 34 weeks (5)	2.6 ∮ (1.8-3.5)	33.5 ∮ (27.2-42.0)	30.9	7.0	0.8	120 ∮ (112-135)	49.8 ∮ (36-67)	3.62 ∮ (3.2-4.4)
34 weeks x (2)	4.2	32.6	28.4	3.2	- 0.4	125	29.5	3.80
Delivery + (2)	2.4	38.6	36.2	8.6	1.0	108	46.0	2.70

* Number of studies at each stage in parenthesis.

∮ Range of values obtained is given.

† On hypotensive therapy.

x After onset of toxaemia.

TABLE XXXII

FOREARM VASODILATATION FOLLOWING ARTERIAL OCCLUSION AND EXERCISE

HYPERTENSIVE SUBJECTS

Stage of Pregnancy*	MEAN Forearm Blood Flow ∮		MEAN Increment Blood Flow				MEAN ∮ B.P.	MEAN Peripheral Resistance ∮	
	Resting	Peak	Peak	After 3 mins	After 10 mins	TOTAL		Resting	Peak
	ml/100 ml tissue/min		ml/100 ml tissue/min			ml/10 mins		mm Hg/ml/100 ml tissue/min	
TWINS WITH TOXAEMIA									
a) 32 - 36 weeks (7)	2.1 (1.1-2.7)	27.7 (20.1-35.8	25.6	5.9	0.8	-	99 (90-117)	51.6 (33-94)	3.70 (2.5-5.1)
PATIENTS ON HYPOTENSIVE THERAPY									
b) Under 30 weeks (4)	2.0 (1.5-2.9)	36.4 (31.0-44.0	36.4	5.5	0.8	-	97 (78-113)	52.6 (27-73)	2.61 (1.9-3.6)
31-Delivery (5)	2.4 (1.6-3.2)	29.9 (28.8-31.2)	27.5	4.1	0.9	-	121 (105-130)	54.2 (38-78)	4.05 (3.6-4.3)
After Deliv. (3)	2.6 (1.9-3.3)	34.3 (26.8-40.2)	31.7	5.5	1.4	-	120 (111-127)	48.3 (39-64)	3.53 (3.0-4.1)
B.P. 120 mm Hg OR OVER									
c) 29 - 39 weeks (14)	3.2 (1.1-6.9)	37.5 (22.1-52.0)	35.3	8.9	1.6	88.0	125 (120-141)	48.7 (17-109)	3.56 (2.1-4.4)

* Number of studies at each stage in parenthesis. ∮ Range of values obtained is given.

TABLE XXXIII FOREARM VASODILATATION FOLLOWING ARTERIAL OCCLUSION AND EXERCISE

PREVIOUS TOXAEMIA

Stage of Pregnancy*	MEAN Forearm Blood Flow ∅		MEAN Increment Blood Flow				MEAN ∅ B.P.	MEAN Peripheral Resistance ∅	
	Resting	Peak	Peak	After 3 mins	After 10 mins	TOTAL		Resting	Peak
	ml/100 ml tissue/min		ml/100 ml tissue/min			ml/10 mins		mm Hg/ml/100 ml tissue/min	
Under 18 weeks (5)	1.8 (1.3-2.3)	25.6 (17.8-38.4)	23.8	4.9	0.1	52.5	83 (73-87)	46.7 (38-64)	3.46 (2.3-4.9)
18 - 30 (8)	2.1 (1.4-2.9)	29.1 (20.6-36.0)	27.0	7.0	0.4	62.6	81 (73-90)	40.9 (28-58)	2.87 (2.0-4.0)
31 - 34 (6)	1.9 (1.3-2.8)	34.2 (25.0-60.0)	32.3	5.8	1.3	68.5	83 (73-93)	46.6 (31-69)	2.60 (1.5-3.2)
37-Delivery (6)	1.8 (1.3-2.0)	30.7 (18.1-37.0)	28.9	5.3	0.6	54.2	84 (73-100)	48.3 (38-59)	2.93 (2.2-5.0)
Delivery - 1 week (4)	2.1 (1.6-2.9)	22.7 (10.3-32.0)	20.6	5.0	0.2	48.5	80 (73-87)	40.0 (28-46)	3.03 (2.5-3.3)
6 weeks + (4)	2.3 (1.8-2.5)	27.1 (19.0-38.2)	24.8	4.6	0.4	51.6	82 (70-87)	37.2 (28-48)	3.32 (1.8-4.6)

* Number of studies at each stage in parenthesis.

∅ Range of values obtained is given.

EFFECT OF ARTERIAL OCCLUSION AND EXERCISE

ON FOREARM BLOOD FLOW

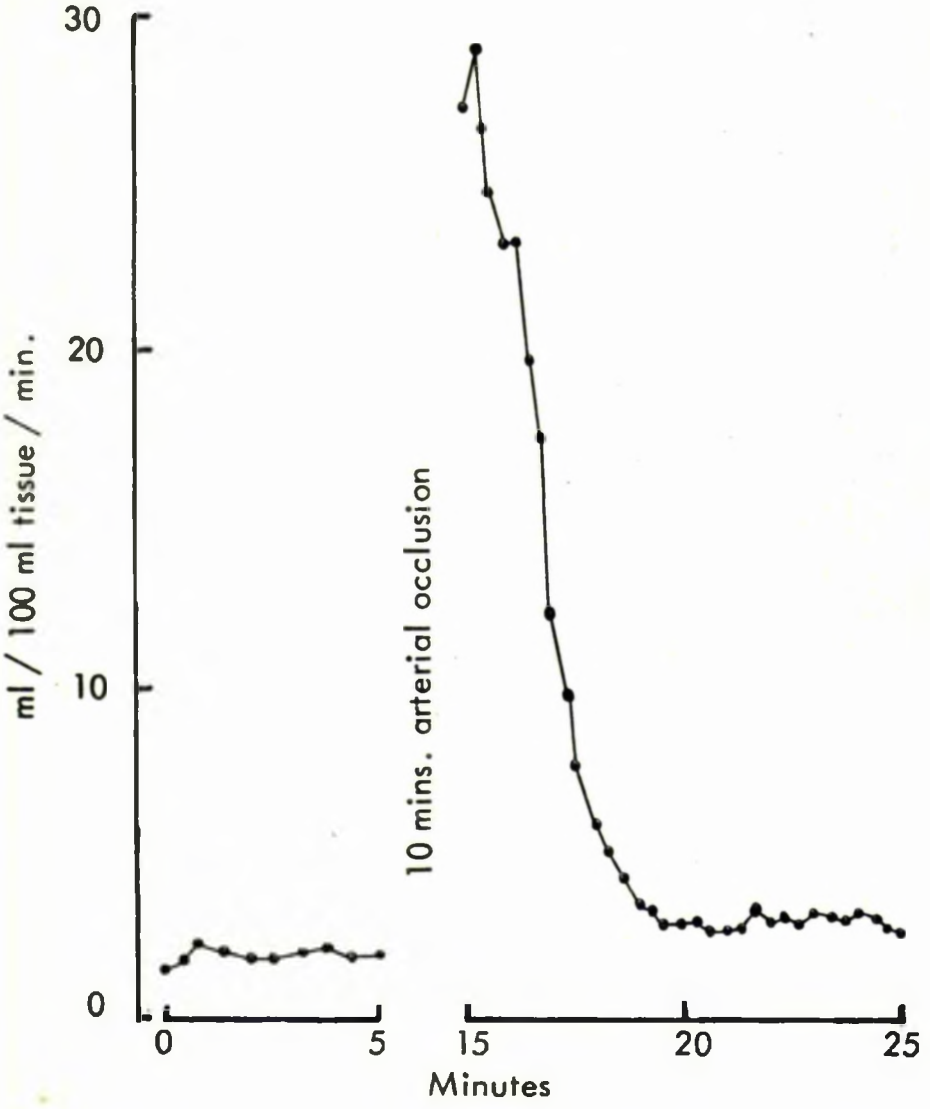


Fig. 26. Forearm blood flow after ischaemia and local exercise, in a normotensive healthy pregnant subject.

Decrease of forearm blood flow from the peak occurs rapidly in an approximately exponential manner (Fig. 26). After ten minutes the rate is usually close to the control flow. In order to compare the increment in forearm blood flow and the rate of decrease towards resting values at different stages of gestation in the various groups, the mean flow rates for each stage and group were plotted on a linear scale at quarter minute intervals. The area of the curve obtained, less the extrapolated resting flow, was measured with a compensating planimeter. Since the scale used for each curve was constant, this reading, in square centimetres, could be converted to millilitres of blood. This value is referred to in the tables as the total increment blood flow per 100 ml tissue over the ten minute period of recording. The curve of increment flow is not provided for each group, but in each table the increment in blood flow over the resting value at the peak level, at three minutes after release of arterial occlusion and at the end of ten minutes is given.

The average blood pressure obtained during each recording was used to obtain the mean blood pressure (diastolic pressure plus one-third of the pulse pressure) and the average for each group is given in the tables. The peripheral resistance at both resting and peak flow rates was calculated by dividing the mean blood pressure by the relevant flow. The tables give the mean for each group of the individual peripheral resistances thus obtained.

In each table, the range of values obtained is given for resting

and peak forearm blood flow, mean blood pressure and peripheral resistance. Comparison of the means of appropriate groups has been made using Student's t-test, the level of significance being taken as 0.05 or less.

Some of the salient features comparing the different diagnostic sub-groups are illustrated in Figures 27 - 33 and referred to in the text.

RESULTS

A - NORMOTENSIVE WOMEN - SINGLE PREGNANCY

The results obtained in 77 studies in healthy women are given in Table XXVI. There were 12 primigravidae and 4 multigravidae. No patient who developed any complication of pregnancy is included. The findings have been analysed according to the stages of gestation and an average taken of the studies made during each four week period of pregnancy, those before 18 weeks of pregnancy being grouped together. After delivery, the mean values were calculated for the following groups:-

(i) within 24 hours of delivery

(ii) after 24 hours to the 7th day

(iii) first to second week after delivery

(iv) at least 6 weeks after delivery.

Within the first half-minute of release of occlusion after ischaemia and exercise, blood flow increased about ten to fifteen times. The mean figures show a lower peak flow between 23 and 30 weeks of

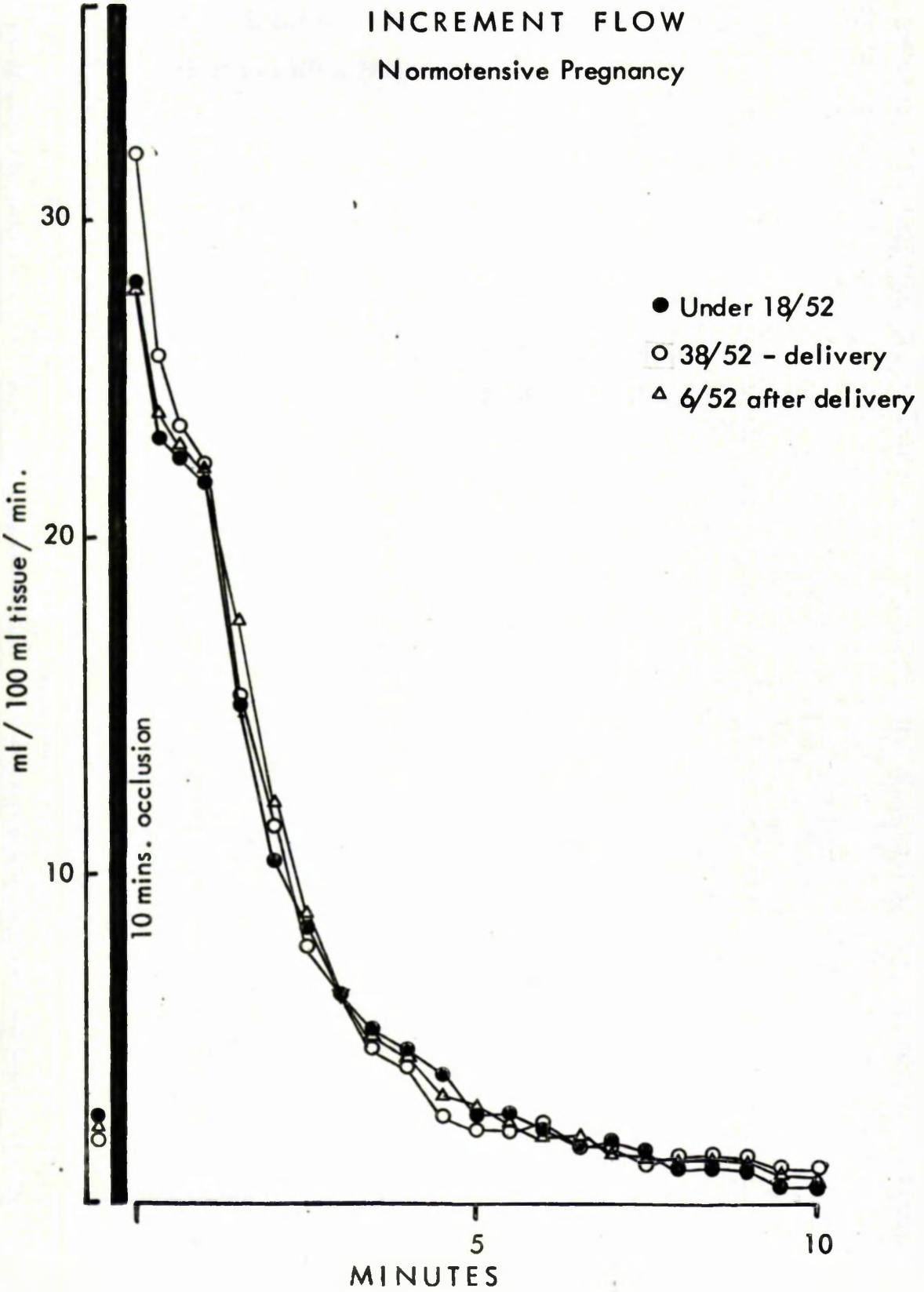


Fig. 27. Mean values of increment forearm blood flow obtained at three of the stages studied in normotensive women. In order to compare the increments only, the resting forearm flow was subtracted. This is shown for each group on the left of the diagram.

pregnancy compared with early pregnancy but the difference is not significant ($t = 1.287$, $P > 0.2$). The peak flow in late pregnancy was close to that found in early pregnancy and in the puerperium. Thus, the mean control and peak flow rates were essentially constant throughout pregnancy and the puerperium. Similarly, the peak increment flow was essentially constant throughout pregnancy and the puerperium. When the increment flow curves for each stage of pregnancy were superimposed, the rates of return of flow to resting values at different stages of pregnancy lay close together. There was a slight increase in the increment of flow ten minutes after release of occlusion in late (35 weeks to delivery) pregnancy but comparison of the values obtained with those obtained from 27 - 34 weeks showed no difference ($t = 0.352$, $P > 0.7$). Fig. 27 shows the increment curves obtained in early pregnancy, late pregnancy and six weeks after delivery.

As described in the previous section, the slight rise in mean blood pressure in late pregnancy and the immediate puerperium is associated with constant forearm flow, the peripheral resistance being correspondingly increased. During vasodilatation after release of arterial occlusion, the peripheral resistance at the peak flow tended to remain essentially unchanged, the slight increase in mean blood pressure being associated with an equally slight increase in maximal blood flow. The changes are, however, minor.

Hence, this study shows that in normotensive women with a normal, single pregnancy, there is no change in the response of the forearm arterioles to a vasodilator stimulus throughout pregnancy and the puerperium.

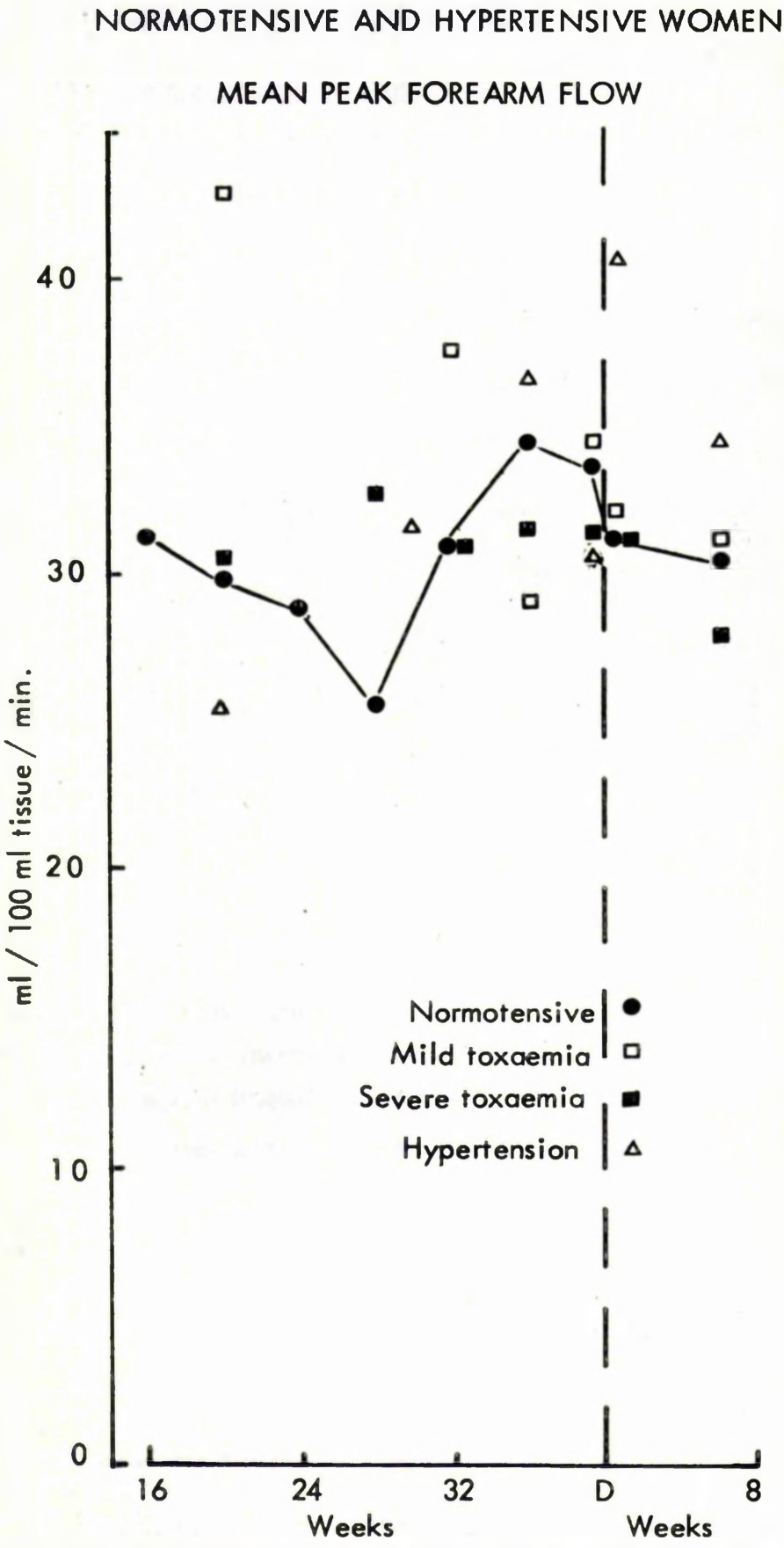


Fig. 28. Mean peak forearm flow during vasodilatation in the different diagnostic groups.

B - NORMOTENSIVE WOMEN - MULTIPLE PREGNANCY

Nine patients with twin pregnancy - 7 primigravidae and 2 multigravidae - were studied on 21 occasions. One patient with triplets was also studied once. Measurements were made from 26 weeks of pregnancy until 2 weeks after delivery. The results are shown in Table XXVII. Control and peak flows, rate of fall in blood flow, total increment flow, mean blood pressure and peripheral resistance at both resting and peak flow rates were all close to the corresponding values in single pregnancy. As found in late pregnancy with a single foetus, there was a slight increase over resting flow at the end of ten minutes.

C - HYPERTENSIVE PREGNANCY

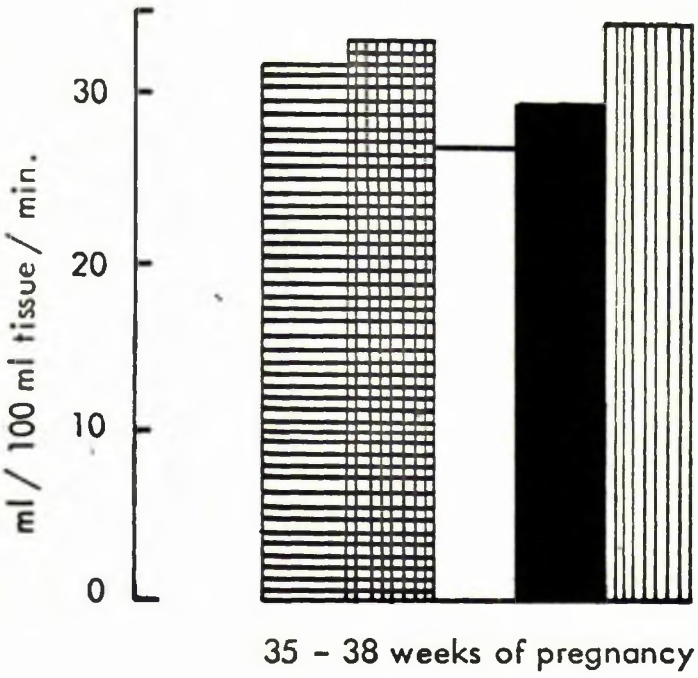
The results are tabulated according to the clinical classification previously described (p. 127). Studies carried out during or within two weeks of hypotensive therapy have been excluded from the main analysis of each group.

(i) Mild Toxaemia

Thirteen patients with mild toxaemia - 10 primigravidae and 3 multigravidae - were studied on 44 occasions (Table XXVIII). Measurements were made before the onset of toxaemia in two patients (Nos. 82 and 90) on account of a previous history of toxaemia. Resting flow is unchanged compared with normotensive women. Peak flow is slightly increased in the recordings made before the 34th week of pregnancy (Fig. 28) but between 35 and 38 weeks when the numbers are larger and

Fig. 29. NORMOTENSIVE AND HYPERTENSIVE WOMEN

INCREMENT OF PEAK FOREARM FLOW



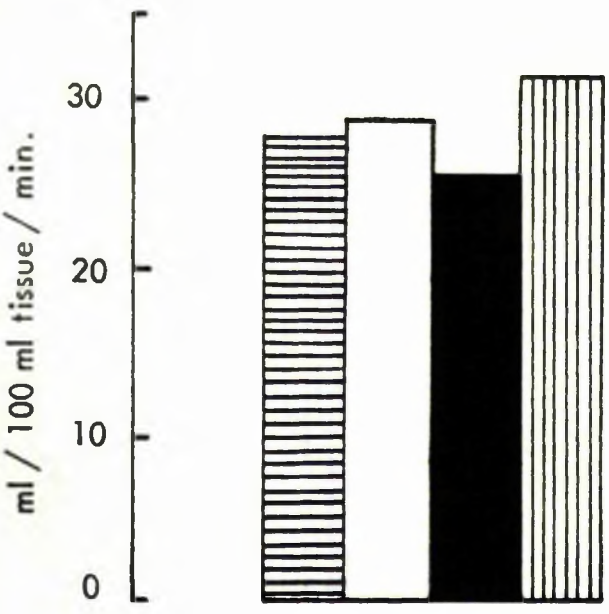
Normal

Twins

Mild tox.

Severe tox.

Essential hypertension



the condition established there is no increase (Fig. 29). Similarly, there is no difference in peak flow between this group and normotensive women in the studies made at least six weeks after delivery.

Fig. 30 shows the total increment flow in late pregnancy (31 weeks to delivery) in all groups. The values in mild toxaemia are close to those in normotensive women.

There is an increase in peripheral resistance (Table XXVIII) at both resting and peak flows. Analysis of the values obtained in mild toxaemia at 35 - 38 weeks compared with the normotensive women at the same stage shows that the increase in resistance is not significant at resting flow ($t = 1.303$, $P > 0.2$) but is significant at peak flow ($t = 2.38$, $P < 0.05$). As shown in the previous section, the peripheral resistance at least six weeks after delivery is higher at resting flow. The increase in resistance at the peak flow is not statistically significant ($t = 2.04$, $P > 0.05$).

Essentially, therefore, in the patients who developed mild toxaemia the increase in mean blood pressure is associated with an increase in resistance, the flow remaining constant at both resting levels and after vasodilation.

(ii) Severe Toxaemia

Fifty studies were made in 13 patients - 9 primigravidae and 4 multigravidae - and the results are shown in Table XXIX. One patient (No. 105) was studied from early pregnancy and the 3 studies under 26 weeks of pregnancy all refer to this one subject before the onset

NORMOTENSIVE AND HYPERTENSIVE WOMEN
TOTAL INCREMENT FOREARM FLOW
IN LATE PREGNANCY

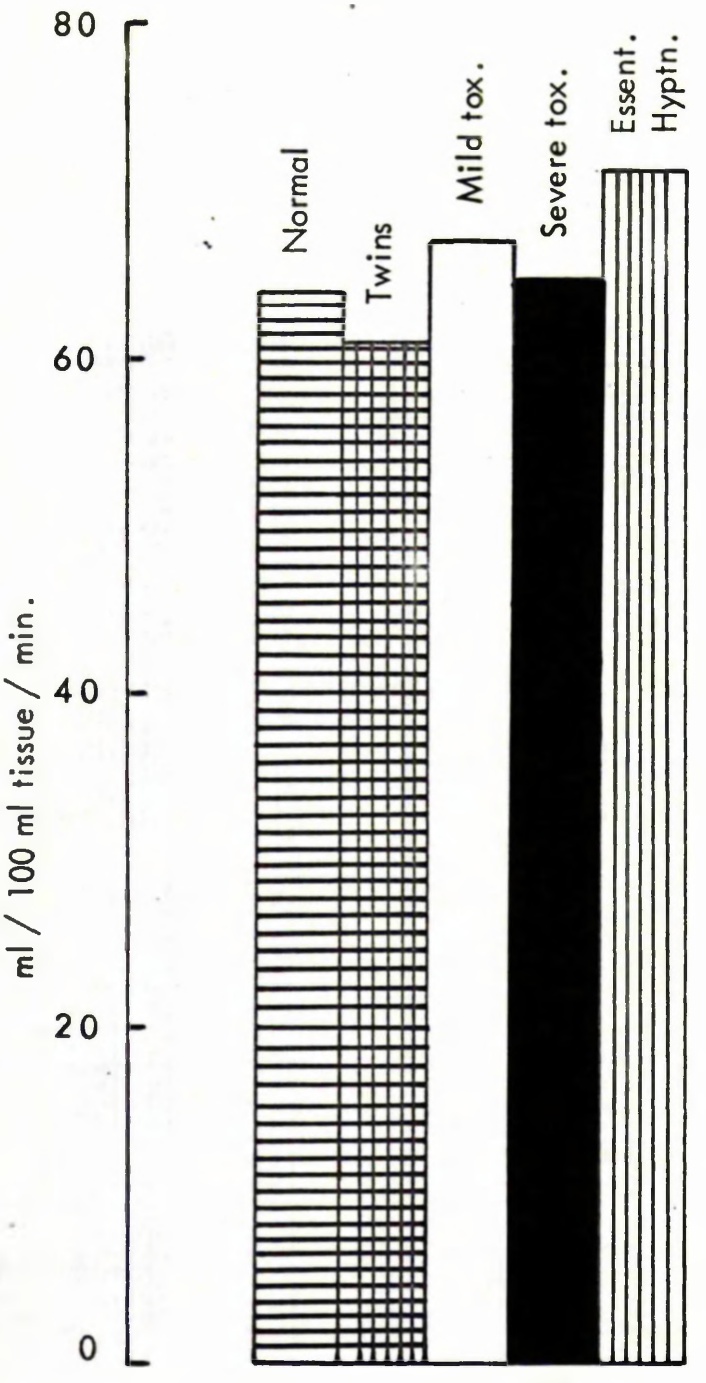


Fig. 30. Total increment forearm flow during the ten minutes after arterial occlusion in each diagnostic group, from 30 weeks of gestation until delivery.

of toxaemia which developed at 29 weeks. The results in the tables from 27 weeks onwards all refer to women studied after the onset of toxaemia, although the severity was not necessarily established at the time of the earliest recordings. However, within each stage, the mean blood pressure is considerably higher than in the mild toxaemia group. The mean values for resting forearm flow, peak and total increment flows differ little from those obtained in normotensive pregnancy. The different diagnostic groups are compared in Figs. 28, 29 and 30. When the mean blood pressure is increased there is a corresponding increase in resistance at both resting and peak flows. Comparing the individual values with those obtained in normotensive women, there is a significant increase in resistance at peak flow at 31 - 34 weeks ($t = 2.593$, $P < 0.05$) and in the larger group at 35 to 38 weeks the increase in resistance is significant at both resting ($t = 2.442$, $P < 0.05$) and peak ($t = 2.84$, $P < 0.05$) flow. There was a further increase in resistance in the 3 subjects whose pregnancy reached 39 weeks.

(iii) Essential Hypertension

The results refer to 39 studies carried out on 9 hypertensive women who did not develop superimposed toxaemia (Table XXX).

There is no change in resting flow, but there is a slight tendency to an increase in peak (Fig. 28) and increment (Fig. 29) flows with a corresponding increase in total flow (Fig. 30). There is a greater increment of flow after ten minutes at all stages compared with

normotensive pregnancy. Compared with normotensive pregnancy there is an increase in the peripheral resistance at resting flow. Analysis of the group studied at 35 - 38 weeks shows that this is significant ($t = 2.220$, $P < 0.05$). Despite the slight increase in peak flow compared with normotensive women the increase in peripheral resistance was maintained at the peak flow rate ($t = 2.603$, $P < 0.05$).

(iv) Hypertension with Superimposed Toxaemia

Two patients with essential hypertension who developed superimposed toxaemia (indicated by the onset of persistent proteinuria) were studied. One (No. 124 in the series) was on hypotensive therapy (Decaserpyl) before the onset of toxaemia. She was delivered at 34 weeks of pregnancy. Table XXXI gives the findings before and after the onset of toxaemia and also in the puerperium. There was a marked increase in resistance in pregnancy and the immediate puerperium, compared with the results some weeks after delivery. The other patient (No. 126) was studied on 7 occasions in pregnancy and 2 in the puerperium and was not on hypotensive therapy. Toxaemia developed at 34 weeks. Caesarean section was performed 24 hours after the onset of proteinuria as foetal growth was already considered to be impaired. The baby, who weighed 3 lbs. did not establish fully independent respiratory function and despite maintained respiration died 7 weeks after birth. The findings in pregnancy have been sub-divided into those before and those after the onset of toxaemia (Table XXXI). Before the onset of toxaemia the results correspond closely to those found in the main group with

essential hypertension. The findings within 24 hours of the development of proteinuria, despite very little additional increase in blood pressure, show an increase in resting flow associated with a fall in resistance, no tendency to delay in return to resting values and no change in peak blood flow. The increase in resistance at peak blood flow compared with normotensive pregnancy was maintained after the onset of proteinuria.

Interpretation of findings in single subjects is difficult but consideration of those two patients and the one (No. 105) who was studied before and after the development of severe toxaemia does not reveal any tendency to a decrease of either resting or peak forearm blood flow with the onset of toxaemia.

(v) Twins with Toxaemia

Two patients (Nos. 128 and 129) with twins developed mild toxaemia in the last trimester of pregnancy. Seven studies were carried out from 32 - 38 weeks of pregnancy (Table XXXIIa). Compared with normotensive twin pregnancy, the resistance is raised at both resting and peak flows, the results being very similar to those obtained in mild toxaemia in single pregnancy.

(vi) Patients on Hypotensive Drugs

5 patients were treated with hypotensive drugs:

Patient No.	Diagnosis	Drug and Stage of Pregnancy Given
92	Severe Toxaemia	10-methoxy-deserpidine ("Decaserpyl") at 32 weeks with delivery a few days later.

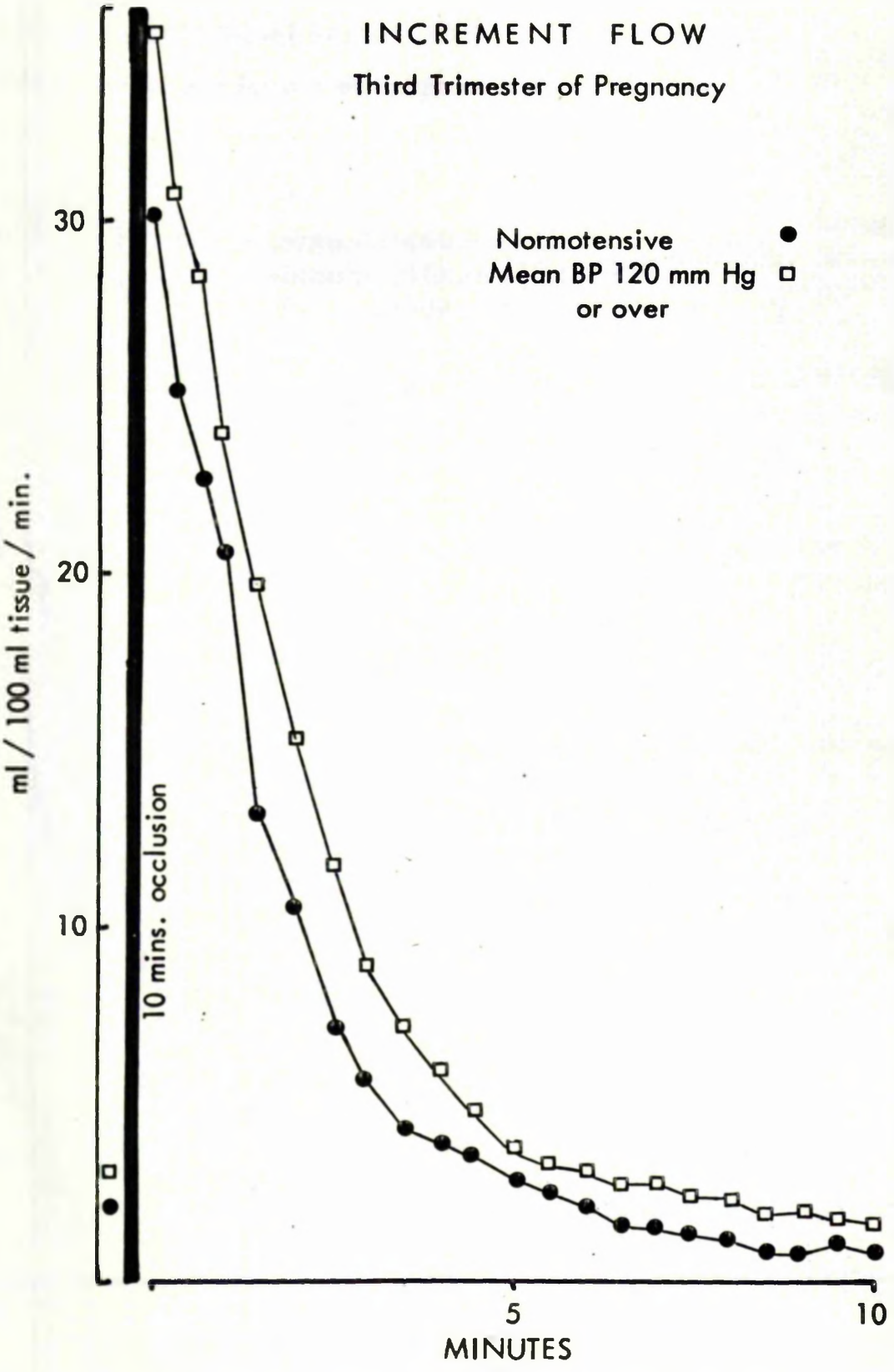


Fig. 31. Mean values of increment blood flow during vasodilatation in normotensive compared with hypertensive women in the third trimester of pregnancy. The resting forearm flow for each group is shown on the left.

Patient No.	Diagnosis	Drug and Stage of Pregnancy Given
111	Essential Hypertension	On ∝ -methyl-dopa ("Aldomet") before, throughout and after pregnancy.
113	Essential Hypertension	On ∝ -methyl-dopa ("Aldomet") from 32 weeks to delivery at 34.
123	Essential Hypertension	On ∝ -methyl-dopa ("Aldomet") from before pregnancy until 29 weeks. None thereafter.
124	Essential Hypertension + Toxaemia	On 10-methoxy-deserpidine ("Deanserpyl") from 33 weeks to delivery at 34 weeks.

Analysis of this heterogeneous group is clearly limited; the values obtained are grouped according to gestation (Table XXXIIb). As in the other hypertensive groups, peripheral resistance at both resting and peak flows is raised.

Since, within the diagnostic groups described, there was considerable variation in the actual level of blood pressure, the findings in all patients (excluding those on hypotensive drugs) who had a mean blood pressure of 120 mm Hg or over at the time of recording have been analysed. Table XXXIIc refers to 14 studies in 10 patients between 29 and 39 weeks of pregnancy. Compared with the normotensive patients at the same stage, there is no reduction in either peak or control flows, both in fact tending to be slightly increased. Resistance is increased

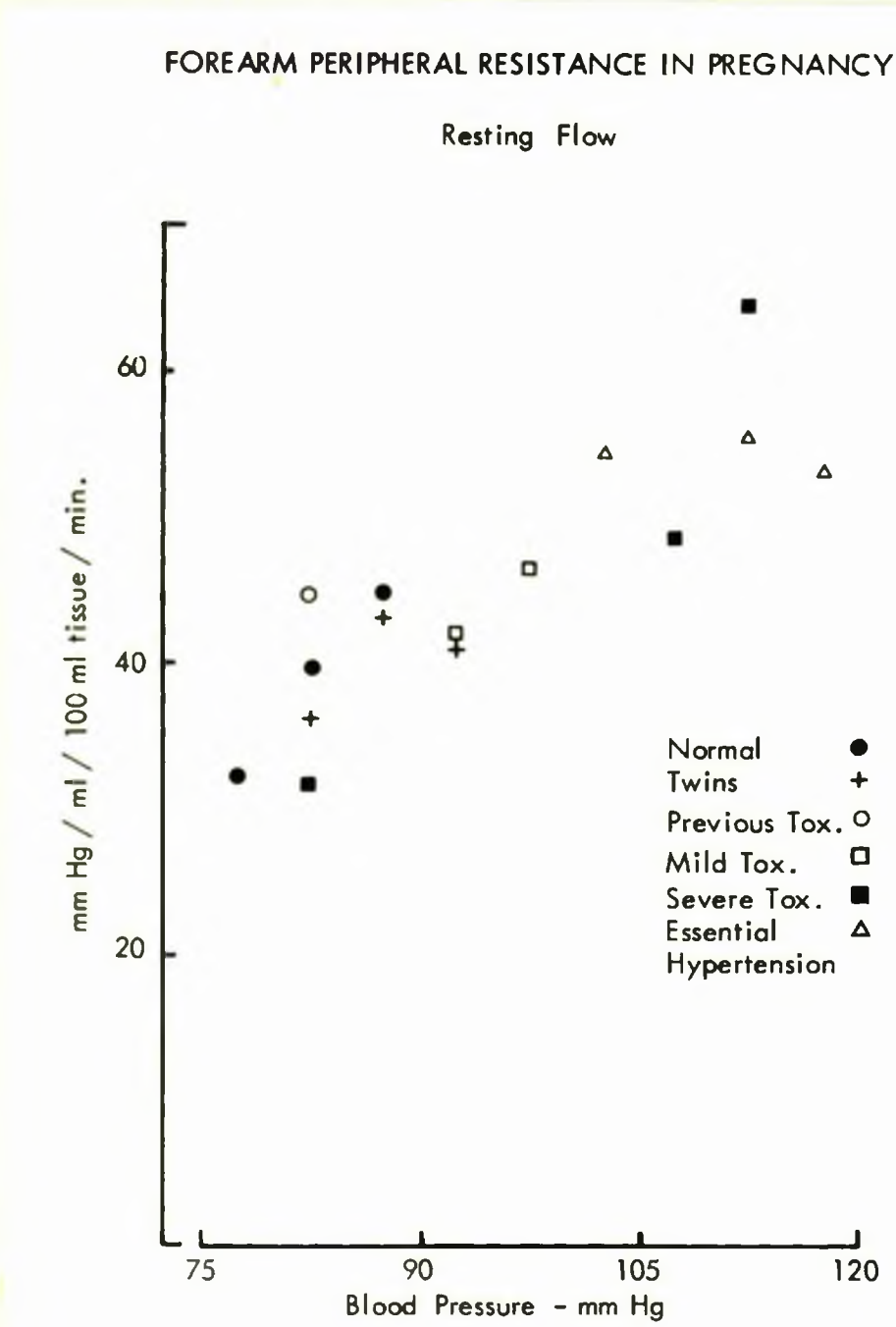


Fig. 32. Relationship between forearm peripheral resistance at resting flow and mean blood pressure, in pregnancy. For a diagnostic group, each point represents all the studies within 5 mm Hg increments in blood pressure, regardless of the stage of gestation.

at both flow levels. The increment curve comparing these patients with the normotensive women at the same stage shows delay in the return of flow to resting levels (Fig. 31). When readings were continued for more than ten minutes after release of occlusion the elevation of flow above the resting value was maintained.

D - PREVIOUS TOXAEMIA

The results (Table XXXIII) refer to 5 women studied on 33 occasions in pregnancy and the puerperium. The findings lie close to those obtained in the normotensive group with no history of toxaemia.

RELATIONSHIP OF PERIPHERAL RESISTANCE AND MEAN BLOOD PRESSURE

To clarify the relation of peripheral resistance to mean blood pressure in pregnancy, the mean resistances at both resting (Fig. 32) and peak (Fig. 33) flow rates were combined according to 5 mm Hg increments in blood pressure regardless of the stage of gestation but maintaining separation within the diagnostic groups. There is a clear association.

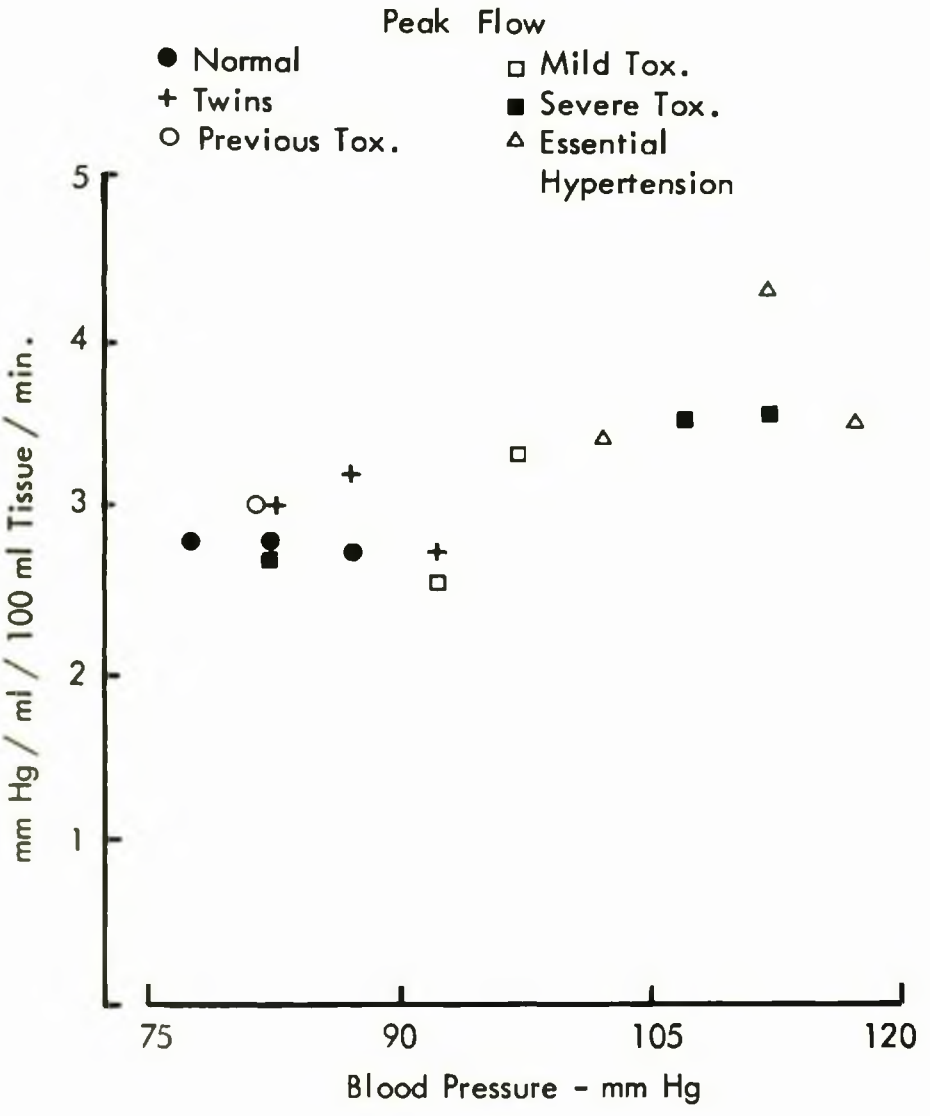


Fig. 33. Relationship between forearm peripheral resistance at peak flow and mean blood pressure, in pregnancy. For a diagnostic group, each point represents all the studies within a 5 mm Hg increment in blood pressure, regardless of the stage of gestation.

SUMMARY OF RESULTS

1. In normotensive women there is no change in resting forearm blood flow or peak blood flow in response to the vasodilator stimulus of arterial occlusion and exercise at different stages of pregnancy. Calculated peripheral resistance at both resting and peak flows shows little variation although a slight increase in mean blood pressure near term and soon after delivery is associated with a corresponding slight increase in resistance at resting flow rates.

2. Similar findings apply to normotensive women with twin pregnancy or with a history of previous toxaemia.

3. In toxaemia of pregnancy the increase in perfusion pressure is associated with an increase in peripheral resistance at both resting and peak flow rates but no increase in flow.

4. In essential hypertension, there is a similar increase in peripheral resistance at both resting and peak flows although there is also an increase in peak flow and an increase in total increment of blood flow over the ten minutes following arterial occlusion.

5. In toxaemia superimposed on hypertension the onset of toxaemia was not associated with a reduction in resting or peak flow rates.

DISCUSSION

MECHANISM OF HYPERAEMIA

Before discussing the factors which may be involved in the response of forearm blood vessels in hypertensive and normotensive pregnancy, present views on the aetiology of the hyperaemia after arterial occlusion and exercise are summarised.

Hyperaemia after ischaemia is not reduced by atropine or sympathectomy (Dornhorst 1963), involves skin and muscle and occurs after denervation, even with gross muscle atrophy (Barcroft 1963). Although the reaction can be obtained in the digits, hand, foot, forearm and calf, it is more reproducible in the latter two segments (Patterson and Whelan 1955).

ISCHAEMIA

The simple and attractive hypothesis that the blood flow during the hyperaemia phase is equivalent to the deficit incurred during ischaemia is not supported by experimental evidence. Thus, Patterson and Whelan (1955) have shown that, whereas indirect heating increases the debt component by increasing the resting forearm flow, the increment of flow above the resting flow during hyperaemia is constant. Also, pressure on the brachial artery after release of occlusion, sufficient to prevent the flow from rising above the resting flow, completely abolishes reactive hyperaemia, provided the partial occlusion is maintained for sufficient time (Blair, Glover and Roddie 1959).

Following a period of ischaemia, lowering the effective local arterial pressure to about 50% by means of a pressure plethysmograph reduces the extent but not the duration of the hyperaemia (Dornhorst and Whelan 1953). Further, lowering a limb after a period of elevation when the flow falls in proportion to the fall in blood pressure is not followed by reactive hyperaemia. Yet, if the blood pressure is reduced to the same extent by occlusion in the limb resting at heart level, reactive hyperaemia occurs (Holling and Verel 1957).

These findings lead to the conclusion that the resting level of limb flow is in excess of metabolic requirements and quantitative replacement of blood after ischaemia is not essential.

METABOLIC FACTORS

Changes in metabolic factors have been considered to have a possible role in the production of hyperaemia.

A change in pH is not considered to be of major importance in the vaso-dilatation of active muscles (Gollwitzer-Meier 1950). Although a slight decrease occurs, the hyperaemia outlasts the pH change (Hilton 1962). The role of excess CO_2 is, however, less clear since Kontos and Patterson (1964) have shown a co-relation between venous p CO_2 and reactive hyperaemia blood flow, although previously, in dogs, the administration of 20% CO_2 had been shown to cause no vasodilatation (Crawford, Fairchild and Guyton 1959). Available evidence (Dornhorst and Whelan 1953, McNeill 1956, Black and Roddie 1958, Hilton 1962) does not suggest that variation in oxygen supply is an important activator

in the production of reactive hyperaemia.

The production of vasodilator metabolites normally washed away by blood but accumulating during occlusion has long been considered to be a probable factor. The main support for this view is the finding that the duration of hyperaemia varies with the duration of ischaemia (Lewis 1927). Potassium has been shown to cause vasodilatation in animal skeletal muscle (Dawes 1941) and may be a factor in the vasodilatation occurring in contracting muscle. However, the amount required to produce vasodilatation is greater than that produced in response to exercise (Kjellmer 1960) and potassium is not, therefore, considered to be the main factor (Hilton 1962). A slightly increased concentration of adenosine tri-phosphate has been found in venous blood after circulatory arrest (Stoner and Green 1945). Abrams, Barker and Butterfield (1965) in a recent study could find no evidence of vasodilator activity in venous blood taken from limbs after various periods of arterial occlusion.

The similarity of the phenomenon of hyperaemia to that following histamine release led Lewis in 1927 to postulate the release of a histamine-like substance, although attempts to demonstrate its presence in the vascular system had not been successful (Lewis and Grant 1925). Further, the administration of an anti-histaminic substance, while abolishing the effect of exogenous histamine, does not abolish reactive hyperaemia (Emmelin and Emmelin 1947, Landowne and Thomson 1948). However, it is possible that histamine release could be a factor in

longer periods of ischaemia since Duff, Patterson and Whelan (1955) found some reduction in hyperaemia with anti-histaminic drugs after arterial occlusion lasting over five minutes.

MYOGENIC HYPOTHESIS

An alternative possible explanation postulates loss of tone in the arterial wall as a result of the fall in intravascular pressure during occlusion.

At the moment of release of occlusion, a greatly increased flow is evident indicating that the resistance of the vessels is very low. This myogenic hypothesis was suggested as long ago as 1902 by Bayliss. The assumption was that the empty vessels relax and hyperaemia occurs during the time necessary for recovery of vessel wall tone. In support of this view, it has been found that reactive hyperaemia can be reduced by elevation of the pressure in the vessels during the period of arrest (Wood , Litter and Wilkins 1955). A similar effect was obtained by trapping blood in the limb by negative pressure (Patterson 1956). The reduction in volume of the hyperaemic flow was found to be greater than the amount of extra blood held in the forearm during occlusion. However, these procedures do not abolish reactive hyperaemia and loss of vessel wall tone is therefore unlikely to be the sole cause.

The present concept, based on the extensive investigations carried out by numerous workers, is that the effect is a local one, independent of nervous control and due to changes in transmural pressure and possibly also to unknown vaso-dilator substances.

Hyperaemia induced by muscle contraction is similar to that following ischaemia although there is evidence that the mechanisms are not identical. Thus, the hyperaemic effect is more prolonged and higher peak flows may be reached (Dornhorst 1963). Maintenance of intra-vascular pressure does not affect the hyperaemia following exercise as it does following ischaemia (Wood, Litter and Wilkins 1955). Local oxygen tension is not an important factor (Dornhorst and Whelan 1953).

In the present study, both ischaemia and local exercise were used in order to provide as strong a vasodilator stimulus as possible in pregnant subjects compatible with their comfort and co-operation. It is probable that the vasodilatation produced was not quite maximal (Folkow et al. 1958). However, additional vasodilatation would have entailed either local or indirect heating or the intra-arterial injection of vaso-dilator substances; procedures which would have involved considerable discomfort and precluded repeated recordings in a series of pregnant woman. Further, to permit comparison of the findings, the technique used in the present study was essentially similar to that employed by Conway (1963b) in a recent study in non-pregnant subjects. Differences in the reaction of hypertensive and normotensive subjects to this type of vaso-dilator stimulus have been interpreted in terms of intrinsic vessel wall behaviour since so many extrinsic factors can be excluded (Folkow et al. 1958, Conway 1963b).

DISCUSSION OF PRESENT RESULTS

INCREASED RESISTANCE WITH DILATATION

The present study has shown that in hypertensive states in pregnancy there is an increase in peripheral resistance in the forearm arterioles which persists during vasodilatation.

A similar increase in resistance has been observed in non-pregnant hypertensive subjects in the forearm (Folkow et al. 1958, Conway 1963b) and in the hand, foot and brain (Stead and Kunkel 1940). In the studies in the forearm there was a slight increase in maximum flow in hypertensive subjects, except in the more severe group where Conway (1963b) found a decrease. The results of the present study are comparable to his less severe group; a finding in accordance with the relatively mild degree of hypertension in the pregnant subjects.

An increase in perfusion pressure in normal subjects, made hypertensive by the intravenous administration of nor-adrenaline or angiotensin produces a substantial increase in peak flow but no increase in resistance (Folkow et al. 1958, Conway 1963b). Thus, the increase in resistance with vaso-dilatation in hypertensive women in pregnancy cannot be attributed solely to a myogenic response of increased vascular wall tone in response to the increase in perfusion pressure. It could be the result of hypertrophy or swelling of the arteriolar wall.

DURATION OF HYPERAEMIA

In the present study, there was, on average, a slight prolongation of hyperaemia after occlusion in hypertensive compared with normotensive

women. When measurements were continued for longer than ten minutes after release of occlusion some elevation of flow was usually maintained for as long as recordings were continued. From the present study alone, it is difficult to evaluate the significance of this increase in hyperaemia in the hypertensive subjects compared with the same stage of normotensive pregnancy. The difference between the groups six weeks after delivery was less than in late pregnancy. However, only four women, with a sustained hypertension of moderately severe degree (mean blood pressure of 120 mm Hg or over) and not on hypotensive therapy were available for study. In the studies in non-pregnant subjects referred to previously (Wilkins and Richna 1941, Folkow et al. 1958, Conway 1963b) the duration and total extent of the hyperaemia were not studied.

Increased production or delayed destruction of vasodilator substances involved in the production of hyperaemia could be responsible for the differences between normotensive and hypertensive subjects in pregnancy. Delay in histamine destruction in this connection must be considered since it has a possible role in hyperaemia following arterial occlusion lasting at least five minutes. Serum histaminase levels tend to be reduced in toxaemia compared with normotensive pregnancy (Kapeller-Adler 1949). However, the marked increase in serum histaminase levels in normal pregnancy (Ahlmark 1944) greatly exceeds variations between different blood pressure states in pregnancy (Koloszynski 1945) and makes it unlikely that variations in histaminase

are important in this connection. It has recently been shown (Lindberg and Tornquist 1966) that, in pregnancy, there is increased activity of diamine oxidase, another enzyme important in the inactivation of histamine but no studies are available in late pregnancy or toxaemia and its possible role cannot at present be assessed. Available evidence does not suggest any alteration in catecholamine metabolism in either normal or toxaemic pregnancy (Swarts, Box and Stevenson 1963, Castren 1964). Plasma renin levels are slightly lower in hypertensive compared with normotensive subjects (Brown, Davies, Doak, Lever, Robertson and Trust 1966) but the significance of this change in relation to peripheral vascular responses is not known.

Thus, there is no clear evidence at present to implicate any particular substance to explain the observed delay in return to resting flow rates in hypertensive subjects in pregnancy.

Toxaemia of pregnancy presents a relatively unusual situation among hypertensive subjects in that the onset of hypertension is rapid and after pregnancy the blood pressure generally falls to normal levels. This study has shown that in respect of flow and resistance the arterioles of toxaemic women behave more as do those in patients with long-standing hypertension than normal vessels subjected to an acute hypertensive stimulus since, in the latter event an increase in flow would be expected. In normal non-pregnant subjects, reactive hyperaemia can overcome the effects of administered vaso-constrictor drugs. If toxaemic hypertension were associated with a generally acting vaso-

constrictor substance effectively raising the blood pressure, it is unlikely that increased resistance would persist on vasodilatation.

There is no evidence in the present results to suggest that before the onset of toxaemic hypertension there is any difference in the behaviour of the arterioles compared with normotensive subjects. Similarly, in the group of women who had a history of previous toxaemia, there was no evidence of any alteration in arteriolar function.

HYPOTENSIVE THERAPY

In the patients included in this study, hypotensive drugs were used purely for maternal indications when the blood pressure was already high or was rising rapidly. The dosages used were such as to control the elevated blood pressure rather than reduce it to normal levels. It is worthy of note that in the patients studied there was no consistent evidence of a reduction of resistance.

The use of hypotensive drugs in hypertensive diseases of pregnancy has been advocated to lower arteriolar resistance (Garber 1958) but there is no evidence in the present results to suggest that any generalised reduction in arteriolar resistance results. It is known, however, that autonomic blocking agents do not reduce the peripheral resistance to normal (Conway 1963a). The modes of action of currently used hypotensive drugs on haemodynamics are complex. Interference with compensatory mechanisms normally invoked during changes of posture and exercise are known to occur (Dollery Emslie-Smith and Shillingford 1961) but there is also evidence that a fall in cardiac output rather than a

decrease in peripheral resistance may be a factor at least with some drugs. Thus, even at rest, a reduction in cardiac output with guanethidine (Richardson, Wyse, McGee and Cavell 1960) and chlorothiazide (Conway and Lauwers 1960) have been shown. The evidence concerning other drugs in current use is inconclusive (Sannerstedt, Schröder and Werkö 1966).

While these observations cannot be directly extrapolated to the uterine vessels they lend no support to the hope, long cherished by obstetricians, that reduction of a raised blood pressure in pregnancy might be associated with an increase in uterine blood flow (Agar and Barrett and Exley 1958). Available studies of clearance of ^{24}Na from the chorio-decidual space do not provide evidence that a reduction of blood pressure is associated with an increase in clearance (Dixon, McClure Browne and Davey 1963). Clinical studies, although achieving satisfactory reduction in maternal blood pressure (Hans and Kopelman 1964), provide no evidence that foetal growth and survival are thereby improved (Townsend 1963).

Thus, unless a drug is associated with reduction of resistance to normal either selectively involving the uterine vessels or occurring generally with cardiac output maintained, a fall in perfusion pressure might well be associated with a reduction, rather than an increase, in uterine blood flow.

This does not, however, exclude the possibility that lowering an elevated blood pressure to normal levels before or early in pregnancy

might prevent the development of organic changes in the vessels of the placental bed with consequent improvement in foetal survival (Kincaid - Smith 1966). Studies of histological changes in the placental bed from patients so treated are not yet available. A recent clinical report showed a successful foetal outcome in women with severe hypertension treated throughout pregnancy with α methyl-dopa (Hamilton 1966).

The present study showing that in normotensive subjects who later develop toxaemia or who have had hypertension in a previous pregnancy peripheral resistance is normal, is at least encouraging in this respect.

CONCLUSION

Since there is an increase in peripheral resistance in hypertensive pregnancy, maintained during a stimulus which normally overcomes neuregenic influences or constricting agents, it is concluded that the vessel wall itself is abnormal. In toxaemia of pregnancy the abnormality is apparently reversible for, when the blood pressure returns to normal, the raised peripheral resistance falls.

PRESENT STUDY - SECTION III

VENOUS TONE IN PREGNANCY IN HEALTHY WOMEN AND IN THOSE WITH HEART DISEASE

VENOUS TONE IN PREGNANCY

GENERAL IMPORTANCE OF THE VENOUS SYSTEM

Despite the upsurge of interest in haemodynamics in recent decades, the venous system has attracted less attention than its importance warrants. Although the veins contain 65 - 75% of the circulating blood volume (Green 1950), their behaviour and control have been relatively poorly studied.

Most of our knowledge of the basic properties of the venous system has been obtained from animal experiments (Alexander 1954, Mellander 1960). In recent years, however, studies in man of the responses to various types of stimuli have shown that the veins are reactive to both generalised and local stimuli (Burch and Murtadha 1956, Bekstein and Horsley 1960, Sharpey-Schafer 1961, Gilbert and Stevens 1966). The effects of humoral agents (Sharpey-Schafer and Ginsburg 1962) and psychogenic stimuli (Burch and De Pasquale 1965) have also been observed. In reviewing some of the recent studies, Folkow and Mellander (1964) claim that in their capacitance function, the veins tend to subserve the cardio-vascular system as a whole rather than the needs of particular tissues.

Vascular 'tone', which may best be regarded as the state of activity of the vascular wall, due partly to intrinsic automaticity and to locally acting metabolic factors and modified by centrally-governed sympathetic constrictor fibres, shows considerable variation between vessels of different structure and region (Folkow 1960). Thus, in

the venous system, the extrinsic vasoconstrictor nerve supply is more important than the intrinsic myogenic tone, enabling the venous system to act as a vascular 'multi-unit', primarily to regulate filling of the heart. This control is in contrast to the resistance side of the circulation where there is intrinsic myogenic tone of varying extent, allowing considerable blood flow reserve in response to local demands. Basal tone is greater in more vital organs, such as the heart and brain. Nevertheless, on the venous side, there is some myogenic activity of the venules, enabling them to vary local resistance (Folkow 1962).

A differential effect of vasoconstrictor fibre stimulation on the capacitance and resistance elements of the circulation has been shown to occur in animals. As vasoconstrictor fibre activity increases, the maximum effector response occurs earlier in the capacitance than in the resistance section of the circulation. Thus, at physiological rates of sympathetic stimulation, which are relatively low, a greater percentage effect occurs on the capacitance side (Mellander 1960). An example of the usefulness of this mechanism is in response to haemorrhage where, with increased sympathetic discharge, constriction of the capacitance section of the vascular bed will tend to proceed that of the resistance section, thus preventing pooling of blood and increasing venous return (Folkow and Mellander 1964).

Hypoxia is one of the stimuli which causes venous constriction and thus increases venous return (Eckstein and Horsley 1960). Some of the clinical conditions in pregnancy which are liable to be associated

with hypoxia, for example, rheumatic heart or chronic pulmonary disease, may also involve an impaired myocardium which might therefore be less able than a healthy heart to accommodate a resulting increase in venous return. In understanding circulatory changes in these patients, any underlying alteration in venous behaviour during or after pregnancy must be considered.

The state of the post-capillary vessels is important in determining capillary filtration. An increase in the ratio of pre to post-capillary resistance, as would result from active dilatation of veins without concomitant arteriolar dilatation, would result in a fall in capillary pressure with resulting inflow of extra-vascular fluid. This mechanism could be important in pregnancy. Since it has been shown in Section I of the present thesis that arteriolar vasodilatation in the limbs in pregnancy is confined to the terminal segments and is not generalised, differential behaviour resulting from any widespread change in venous tone would have important effects on the cardio-vascular system.

Hence, a study of the behaviour of peripheral veins in healthy women in pregnancy was considered to be an essential part of the investigation of peripheral circulatory changes and was carried out as a parallel study with the measurement of limb blood flow.

CURRENT VIEWS ON THE ROLE OF THE VENOUS SYSTEM IN PREGNANCY

Reduction of tone in the walls of veins, assumed to be due to pregnancy hormones, has frequently been considered a factor in the aetiology of varicose veins in pregnancy (Browne and McClure Browne 1963, Wilson Clyne 1963, Cunningham 1964). It has further been claimed that marked symptoms of varicose veins may occur as a result of hormone therapy to prevent abortion (Tenney and Little 1961). However, the increase in venous pressure which occurs in the leg but not in the arm in pregnancy (Burwell 1938) is a direct result of obstruction to venous return (Brigden, Howarth and Sharpey-Schafer 1950, Kerr 1965) and is considered of vital importance in the development of varicosities (Baird 1962, Hultain and Kennedy 1957, Johnstone and Kellar 1965). It is, therefore, not established that intrinsic changes in the walls of veins occur in pregnancy.

In regions associated with increased vascularity, for example the breasts and pelvic organs, greater venous filling is obvious even in early pregnancy, but this of itself does not constitute evidence of generalized active venous dilatation. Changes in the calibre of veins do not provide evidence of altered vasomotor function unless the observations are correlated with associated haemodynamic factors (Alexander 1954). Thus, the calibre of a vein is really an indication of a change in volume. This change may be caused by:

a) changes in flow through the peripheral vascular bed

b) alterations in the pressure and/or resistance to flow in

more central portions of the venous channels

c) changes in the extra-vascular tissue pressure, and

d) changes in the venomotor tone.

Unless the first three of these factors are excluded, there is no justification for attributing a change of venous calibre to a change in venous tone (Alexander 1963).

In pregnancy, it is clear that at least the first two of these factors apply to some regions.

Recently Chesley (1966) has interpreted the findings of Assali and his colleagues (1952), that there is a greater reduction of blood pressure with autonomic blockade in pregnant compared with non-pregnant subjects (discussed on p. 17), to mean that there is <u>increased</u> neurogenic tone of the capacitance vessels in pregnancy. However, in view of the passive effect of obstruction to the inferior vena cava and the altered distribution of cardiac output in pregnancy, such a conclusion is not warranted in the present state of knowledge concerning direct behaviour of the veins in pregnancy.

<u>PREVIOUS STUDIES IN PREGNANCY</u>

McCausland, Hyman, Winser and Trotter (1961) have studied venous distensibility in the finger-tip in pregnancy using a plethysmographic method. A venous congesting pressure was applied immediately proximal to the finger-tip plethysmograph and arterial occlusion to the arm above the elbow. The volume changes in the finger-tip at congesting pressures ranging from 20 - 60 mm Hg at 10 mm Hg increments were then measured.

The volume variation at an arbitrary increase of 30 mm Hg from the initial point of effective pressure, obtained for each subject, represented the venous distensibility for that particular test. A mean increase of 150% in venous distensibility in late pregnancy was shown, with a return to early pregnancy levels 8 to 12 weeks after delivery. However, this increase near term was the mean of the findings in only five women without, and four with, varicose veins, the latter group showing greater distensibility. There was considerable variation between individual values and also between subjects. Using the same method in a different study in non-pregnant subjects, wide variation between individual control subjects was found (Hyman, Arthur, Trotter, Humphreys and Winsor 1961).

The finger tip has unique vascularisation due to a large number of arterio-venous anastomoses. Since the large increase in hand blood flow in pregnancy presumably involves these structures, it is difficult to be certain that any volume changes measured in the finger tip are solely venous. Furthermore, results derived from measurements in the human hand describe the behaviour of skin vessels in a region with unusual sympathetic nervous control; one cannot infer similar changes in other vascular regions (Gauer and Thron 1962). Additional possible variable factors in the method, which may have influenced the findings, will be discussed later (p.184).

After the present study had begun, Goodrich and Wood (1964) reported increased venous distensibility in the leg and forearm in

pregnancy and during oral contraceptive therapy. Three groups of women were studied, each on one occasion: third trimester of pregnancy, two to three months after delivery and during the administration of oral contraception. Venous pressure-volume curves were obtained in a resting state by step-wise increase of pressure in an upper arm occluding cuff. The resulting changes in volume were measured by a plethysmograph, modified to accommodate a column of water filled to provide sufficient local external pressure on the extremity to counter-balance local venous pressure. This method of 'pressure plethysmography' enables all measurements to start with empty veins.

Both these studies of venous distensibility in pregnancy avoided the insertion of a needle or a catheter into a vein. This omission does, however, involve assumptions concerning venous behaviour and further evaluation of both these studies is made after discussion of the factors involved in the measurement of the venous system and description of the present study.

CRITIQUE OF METHODS OF STUDYING THE VENOUS SYSTEM

The essential feature of the venous system is capacity variation, illustrated by the finding that large changes in flow can occur without any alteration of central venous pressure. The basic properties of the walls of all capacity vessels are passive distensibility and active contractility (Gauer and Thron 1962). Thus, active responses of the veins have to be distinguished from passive reactions during filling. Control of the venous system involves:- the functional characteristics

of its smooth muscles, superimposed nervous and hormonal influences, reflex and central control, co-operation or competition between neurogenic mechanisms and local factors which influence venous tone (Folkow and Mellander 1964). These multiple and sometimes opposing factors complicate interpretation of changes in the aspects which can be measured.

Capacity variation, which reflects changes in venous tone, is more difficult to measure than flow and pressure changes, which are the main variables on the arterial side. Thus, the rate of change and the level of the distending pressure in veins are less useful measurements than in arteries. The pressures are relatively low, which means that hydrostatic factors play a more important part. Correction for this is often difficult due to the collapsible nature of the venous system and the valves, which may result in lack of continuity of the blood column.

Much of the existing knowledge of the behaviour of veins in relation to local arterial inflow has been obtained from animal experiments, notably in cats (Mellander 1960, Mellander and Lewis 1963). However, in order to exclude extraneous factors, most of these studies have been made in animals under anaesthesia, usually eviscerated, sometimes supported by artificial respiration and occasionally deprived of their adrenal glands. Such procedures are not feasible in intact, conscious human subjects who present inherent experimental difficulties, have a vascular system easily influenced by emotional factors and thus

necessitate the use of very different techniques.

In human subjects, most techniques of venous behaviour involve the measurement of both volume changes and pressure. However, whereas the volume of all the tissues in the region under study can be measured, changes in pressure can be recorded only at a particular point and may not be representative of the whole region. Further, a catheter in a vein may obstruct the flow. In investigations of veins involving volume change there is difficulty in obtaining a uniform starting volume. Methods of achieving this usually depend on collapsing the system of the part under investigation by elevation or by applying an external pressure, but this increases the pressure gradient above that normally present.

Three main groups of methods of investigating the peripheral venous system in the human subject have been used. Each has limitations and the main principles are discussed.

1. <u>"Isolated" venous segment</u>

This method has been used to show reflex activity (Burch and Murtadha 1956, Burch and De Pasquale 1965).

A short segment of a superficial veins can be isolated from the circulation using external pressure by metal wedges and changes in pressure studied. While information concerning vasomotor responses has been obtained using this method, there are considerable drawbacks. Only a few subjects have suitable segments, and a very sensitive manometer is necessary since the pressure changes in a short segment

are small. Consequently, artefacts are considerable and any body movement or muscle contraction causes troublesome disturbances. It is difficult to be certain that no small radicals are entering the segment. Above all, the segment is isolated from the circulation and therefore from the influence of any circulating substance.

2. Pressure - Volume Relation

Variations of methods involving this principle have been used by several groups of investigators (Eckstein, Hamilton and McCammond 1958, Wood and Eckstein 1958, Hyman, Arthur, Trotter, Humphries and Winsor 1961, McCausland, Hyman, Winsor and Trotter 1961, Gauer and Thron 1962, Goodrich and Wood 1964, Bevegård and Shepherd 1965, Brown, Greenfield, Goei and Plessaras 1966).

Essentially, the change in volume has been measured at a given congesting pressure when a steady state has been reached. The methods used in both previous studies in pregnancy (McCausland et al. 1961, Goodrich and Wood 1964) are examples of this type of investigation. Difficulties with the techniques include the standardisation of the initial volume, difficulty in reaching a steady state, movement of the subject when slow distension is involved, the possibility of capillary filtration and the random volume changes due to arteriolar activity. In some studies arterial occlusion has been used to obviate some of these variable factors.

3. Venous Pressure Increase per Unit Inflow

This technique was described by Sharpey-Schafer 1961 and has

subsequently been used by several investigators (Sharpey-Schafer and Ginsburg 1962, Mason and Braunwald 1964, Mason and Melmon 1965, Sharpey-Schafer, Semple, Halls and Howarth 1965, Gilbert and Stevens 1966).

It involves simultaneous measurement of the rate of rise of venous pressure related to the rate of arterial inflow. An increase in the rise of pressure per unit of inflow implies constriction of the veins, whereas a decrease implies relaxation. Measurements can be made frequently over short intervals with restoration of the normal circulation between recordings. The method has been criticised (Brown et al. 1963, 1966, Bevegård and Shepherd 1965) on the grounds that the filling rate of veins is not constant and thus the pressure rise is not linear, occurring at different rates in different veins according to the relative rate of blood flow. However, Sharpey-Schafer (1961) found that the initial venous pressure rise was usually linear provided the venous pressure measurement was made in the 5 - 20 mm Hg range. The usefulness of the method has been demonstrated by the alteration of venous tone in a wide variety of conditions: valsalva manoeuvre, venesection, absence of baroreceptor reflexes (Sharpey-Schafer 1961 and 1963), the effect of circulating humoral agents (Sharpey-Schafer and Ginsburg 1962) and postural changes (Gilbert and Stevens 1966).

Consideration of the methods used for studying the venous system in the intact subject leads to the conclusion that all methods have some limitations. Interpretation of the findings must therefore be made with caution.

PRESENT STUDY

In the present investigation, the method used measured the rate of pressure rise per unit of inflow to the region; a technique essentially similar to that described by Sharpey-Schafer (1961). An important advantage is that the normal arterial inflow to the region is maintained during the procedure. The forearm was studied since it is an accessible region where the arterial inflow does not change in the course of gestation and where direct pressure effects due to the enlarging uterus are not operative.

Measurement of the same patient during and after pregnancy was thought to provide the best basis for comparison of changes in venous tone in relation to pregnancy. In most subjects selected, an attempt was made to measure venous tone in early, mid, and late pregnancy, during the first week of the puerperium and several weeks after delivery. When possible, a further measurement was made at least six months after delivery. For various reasons a complete series of records was not obtained in many patients: some women moved out of the area during the pregnancy or soon after delivery, some seemed to be nervous during the first one or two visits, some could not spare the time required, some did not have suitable venous segments for study and in others, after satisfactory insertion of the venous needle application of the plethysmograph interfered with satisfactory recording of the venous pressure. The latter was the commonest single difficulty. Analysis of the results has therefore been made only in those in whom satisfactory

recordings were made on at least two occasions.

HEALTHY SUBJECTS

There were 37 healthy pregnant women in this group and clinical details are given in Table K in the Appendix (Nos. 135 - 171). All were attending the antenatal clinic, volunteered for the investigation and developed no disease of pregnancy. In three patients, labour commenced spontaneously, with no associated cause before 36 weeks of pregnancy; healthy premature babies were born. Labour was induced ten days after term in one patient (No. 147) on account of a previous large baby. Two patients had a Caesarean section after the onset of labour, one for a brow presentation and the other for outlet disproportion. Seven had forceps deliveries (two under general anaesthesia) and two others had assisted deliveries. One patient (No. 145) sustained a third degree tear which was sutured under general anaesthesia. As in the study of limb blood flow, measurements were not made for four days after an operative delivery or when there was pyrexia (oral temperature 99°F or over). The study was carried out over a sufficient period to avoid any seasonal bias.

WOMEN WITH HEART DISEASE

Studies were also made in seven women with rheumatic heart disease (Table L, Nos. 172 - 178). All were functionally Grade I or II (American Heart Association classification) at the time of the investigation. The exact nature and severity of the lesion varied.

Fig. 34. Forearm with needle and plethysmograph in situ for recording venous tone. Arterial and venous occlusion cuffs are in position.

Mitral stenosis was the predominant lesion in five, aortic stenosis in one and mitral incompetence in the other. Valvotomy was performed five years before the pregnancy in one subject and in the mid-trimester of the present pregnancy in two others. Some of these patients were not referred for care until mid- or late pregnancy. Labour occurred at or after term in all the patients in this group. Induction of labour was not performed.

METHOD

Most of the women studied were attending as out-patients. The conditions of rest, position, ambient temperature and post-absorptive state were similar to those used in the study on resting limb blood flow.

The patient was comfortably supported so that the mid-forearm was at the level of the manubrium sterni (Fig. 34). A large vein, with no obvious nearby valve, was selected and a small amount of 1% procaine was injected into the skin with a No. 20 needle over the proposed site of needle insertion. A No. 2 short bevel needle attached to a nylon catheter (internal diameter 0.030 inches) was inserted into the vein. The catheter was connected to a Statham pressure transducer (P 23Dd) and the venous pressure variations recorded on either a photographic or direct writer recorder via a suitable amplifying system (Cardiac Recorders Ltd.). A free flow of blood in the catheter was confirmed and the needle was flushed with heparinised saline at frequent intervals.

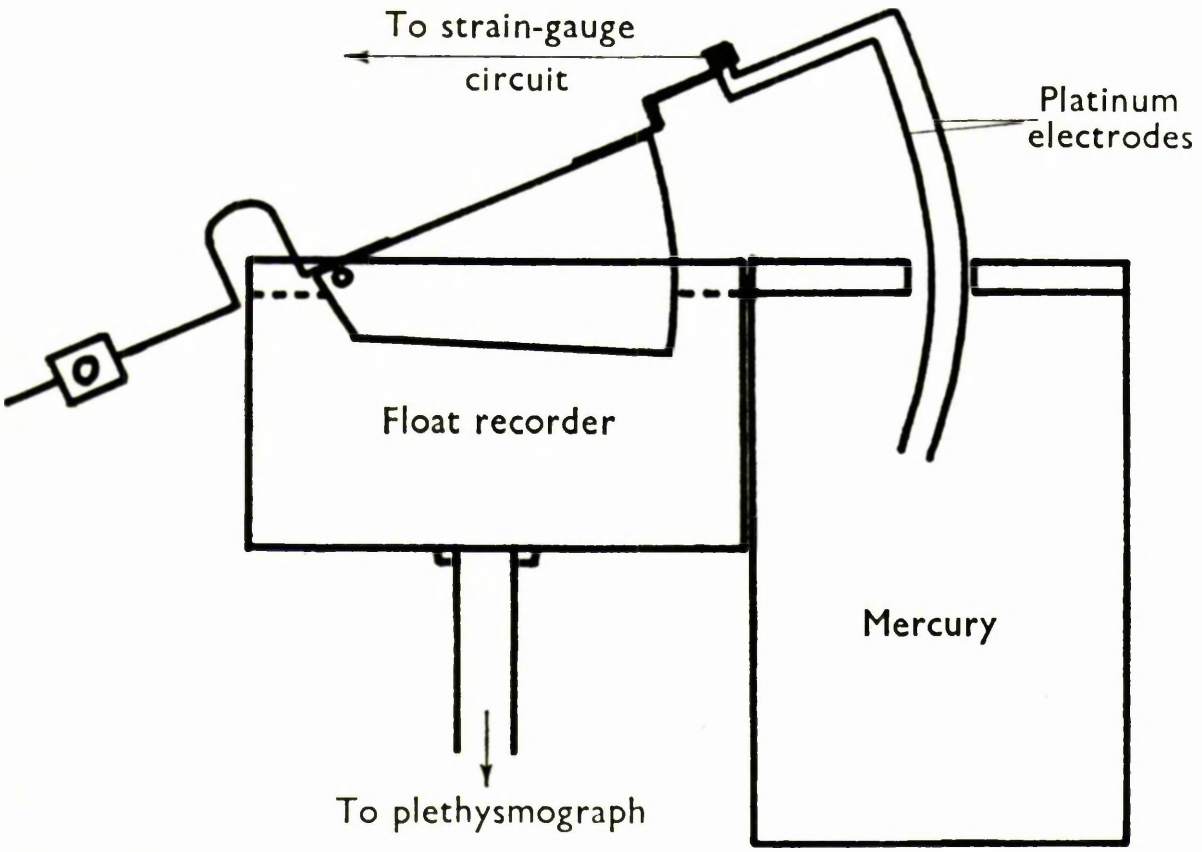


Fig. 35. Diagram of float recorder adapted to record electrically.

Forearm blood flow was measured by a water-filled plethysmograph as used in the studies of limb blood flow. It was positioned so that the venous needle was within the plethysmograph. The level of water in the vertical tube was kept low and the diameter was wide (3.5 cms) so that the increase in hydrostatic pressure on the vein during recordings was minimal. The water in the plethysmograph jacket was maintained at 34 ± 1°C.

On subsequent occasions, the same arm, the same plethysmograph cuff size and, if possible, the same vein were used. If any difficulty was encountered in maintaining a free connection in the vein or in obtaining satisfactory recordings with the plethysmograph in position the procedure was abandoned, since it was considered that any attempts to adjust the venous needle might result in spasm and erroneous results.

In order to record the volume change in the plethysmograph simultaneously with the venous pressure variation on the same recording device, a method other than the usual kymograph recording was required. A suitable method of registering the float recorder variations was therefore devised (Bernard and Duncan 1965).

RECORDING SYSTEM

Using the circuit of a mercury-in-rubber strain gauge, the mercury-filled rubber tube was replaced by two parallel platinum electrodes of similar resistance fixed to the float recorder (Fig. 35). The free ends of the two electrodes were dipped into mercury in an enclosed vessel so that they could move vertically in the mercury throughout the full

range of movement of the float recorder. The change in resistance produced by varying displacement of the platinum in the mercury induced corresponding changes in the strain-gauge circuit.

The system was tested by injection of measured volumes of air (up to 15 ml) into the system. Linearity was obtained when the platinum electrodes were bent to correspond with the curve of the float recorder. Mechanical balance throughout the effective range of displacement of the platinum was obtained by use of a counter-balance.

The method was tested by comparison with a float recorder connected to a kymograph as used in the previously described measurements of limb blood flow. Using a water-filled plethysmograph under standardised conditions, forearm blood flow was measured in seventeen subjects, ten consecutive flows being measured using both the conventional float recorder and the modified one. The order of use was alternated. The average value for each method for each patient was calculated and the results are shown:-

Measurement of forearm blood flow (ml/100 ml tissue/min) using:-

PLATINUM ELECTRODE	KYMOGRAPH PEN
4.4	4.5
4.0	4.0
2.6	3.0
2.5	2.5
2.5	2.4
2.6	3.2
3.4	3.1
3.0	2.9
1.2	1.1
2.4	2.4
3.2	2.7
2.2	2.1

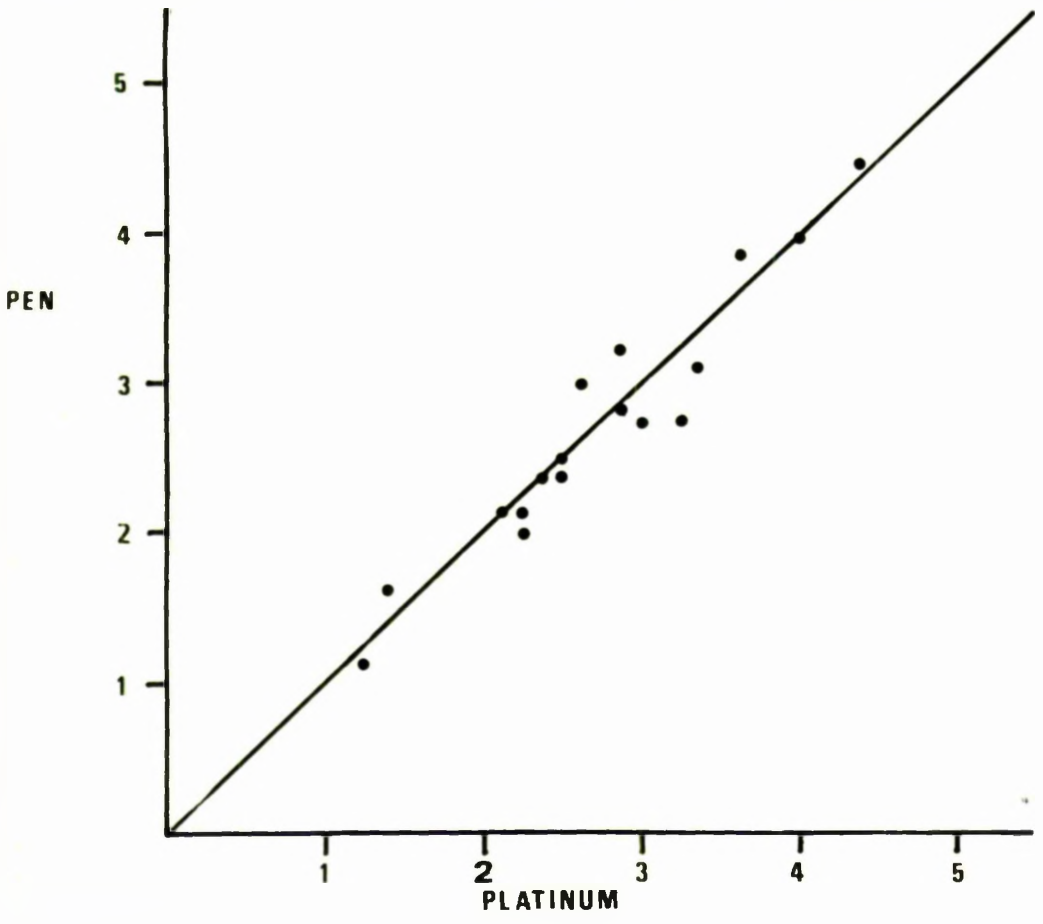


Fig. 36. Comparison of measurements of forearm blood flow in 17 subjects using the platinum electrode recorded electrically and the conventional pen writing on a kymograph.

Measurement of forearm blood flow (contd):-

	PLATINUM ELECTRODE	KYMOGRAPH PEN
	2.2	2.0
	2.1	2.1
	2.9	2.8
	3.4	3.1
	2.8	3.2
Mean	2.76	2.77

Co-relation was found to be close, mean forearm blood flow measured by the kymograph float being 2.77 and by the platinum electrode 2.76. The results for each subject measured by both methods are shown in Fig. 36.

PROCEDURE

With the apparatus in position, a venous occlusion cuff inflated to 60 mm Hg was applied above the elbow. Linearity of both the pressure and flow recordings was checked and any undue artefacts were eliminated by adjustment of the cuffs. The resting venous pressure varied but was always positive and was generally within the 0-5 mm Hg range. A distal arterial occlusion cuff was then applied and a minute allowed to elapse before recordings were made.

Thereafter, a series of pressure-flow recordings was made over several minutes (Fig. 37).

The pulse rate and blood pressure (by auscultation) were recorded at the end of the procedure.

To calculate the venous tone the rate of rise in venous pressure

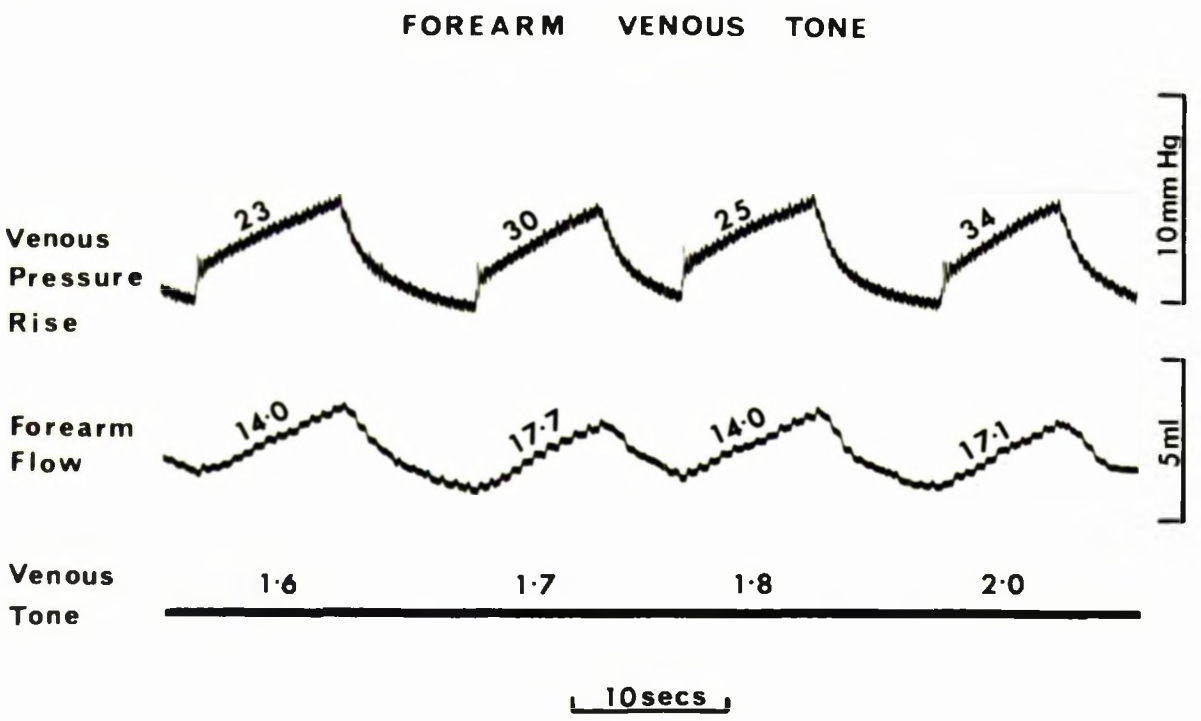


Fig. 37. Recording of forearm venous tone.
The venous pressure rise is expressed in mm Hq / min.
The forearm flow is expressed in ml / min.

The forearm volume was the same for both the pressure and flow increase.

The ratio of pressure / flow gives a measure of the venous tone expressed in arbitary units : mm Hg / ml.

per minute was measured in mm Hg for each venous occlusion and was divided by the rate of arterial inflow to the entire segment in the plethysmograph, expressed in ml/minute, for the corresponding venous occlusion. The resulting factor is expressed in arbitrary units: mm Hg/ml. The average of the series of such ratios obtained for each patient was taken as the measure of venous tone for the particular stage of pregnancy.

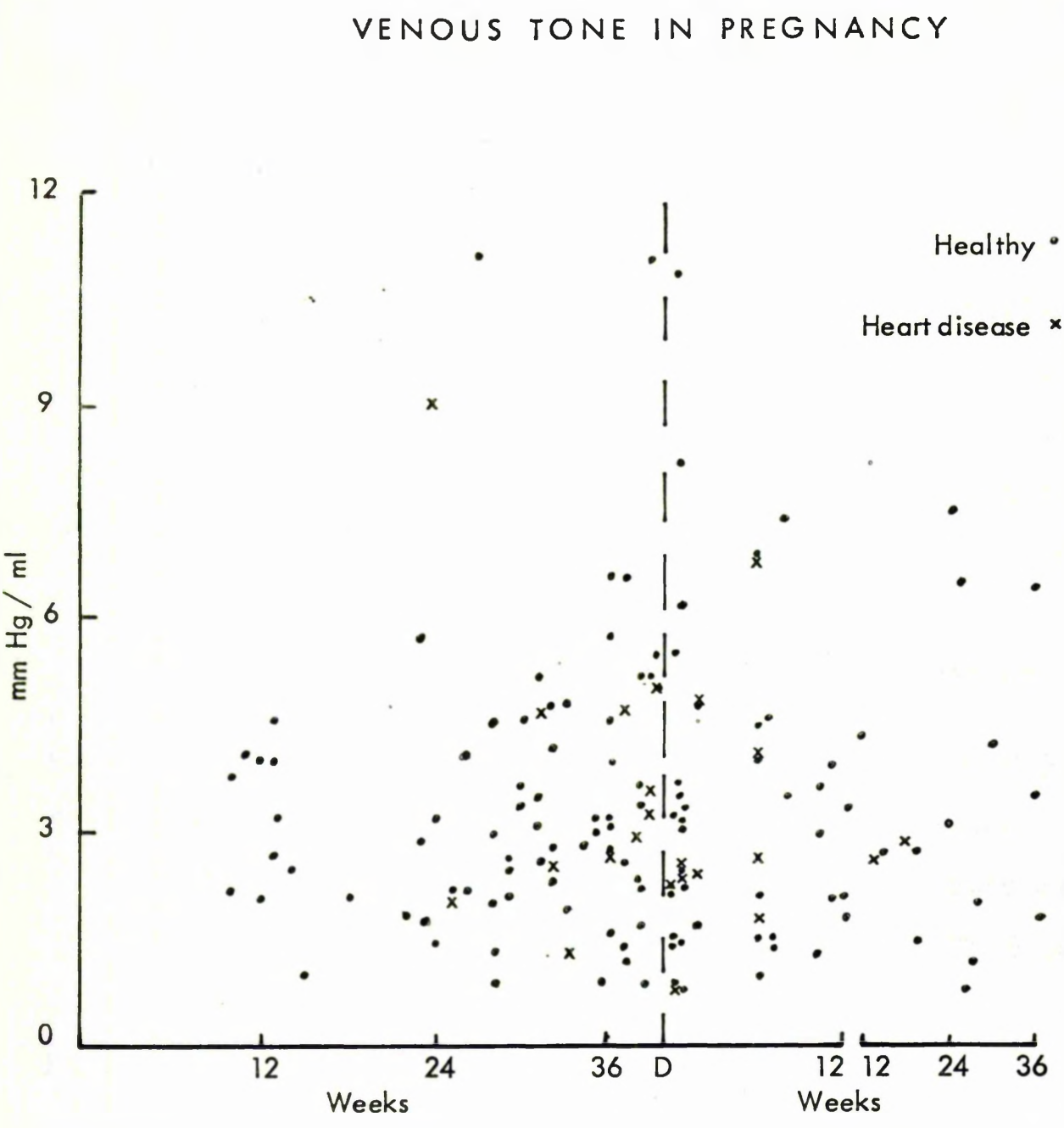


Fig. 38. Values of venous tone during pregnancy and after delivery in both healthy women and those with heart disease.

RESULTS

HEALTHY WOMEN

Measurements were made on 126 separate occasions in the 37 healthy women studied. The results have been sub-divided into three stages in pregnancy and three in the puerperium and are given in Table XXXIV. The individual values shown in Fig. 38 are spread over a considerable range but the mean values show no consistent variation during pregnancy or the puerperium. Fig. 39 relates the individual values for venous tone to the forearm flow rate at the time of measurement. The forearm flow was generally between 1 and 3 ml/100 ml tissue/min although one subject on two occasions had a flow of 7.8 ml. There is no co-relation between the rate of forearm flow and venous tone.

HEART DISEASE

The results of 23 recordings on the 7 patients with rheumatic heart disease are given in Table XXXV and are compared with the normal women in Figs. 38 and 39. The values are close to those obtained in healthy subjects.

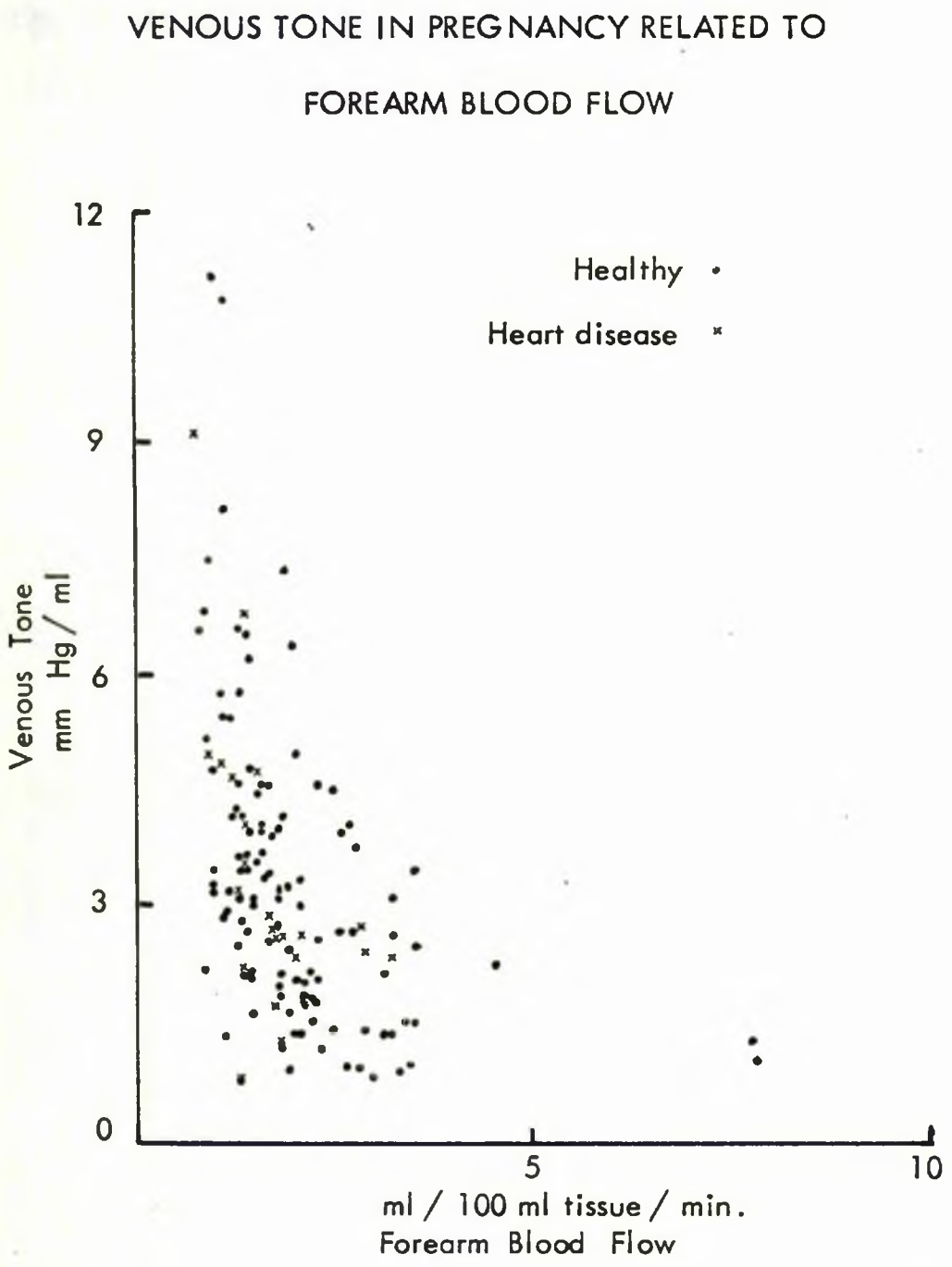


Fig. 39. Values of venous tone during pregnancy and after delivery plotted against the corresponding rate of forearm blood flow for each subject at the time of measurement.

TABLE XXXIV - HEALTHY WOMEN - VENOUS TONE (mm Hg/ml)

Number of Patient in Series	PREGNANCY (Weeks)			PUERPERIUM (Weeks)		
	Under 20	21-30	31-Delivery	Delivery-2	3-16	17+
135	4.1	2.7			2.1	
136	2.5	(5.6	(6.6	1.5	(6.9	
		(4.6	(5.5		(2.7	
137			0.9	0.9		
138				3.2	4.3	
139	4.0	4.2	1.2	3.7		
140		2.2	4.0			4.2
141			(1.9	1.4		1.5
			(2.8			
142			1.4			2.7
143		2.2			7.4	
144		1.5	2.6		2.1	
145		4.1	11.1	8.2	4.5	6.5
146			1.6	0.8		
147	4.0	2.5	1.4	1.7		
148	1.0	3.7	3.0	5.5		
149		11.1	3.1	2.2		1.3
150		3.5		2.2	2.1	
151				1.0	1.2	
152			2.3		1.4	3.5
153	4.6		(4.8	2.2		
			(3.8			
154			3.2	6.2		
155		1.4			1.5	
156			5.0	10.9		1.8
157	2.1		(4.8	3.5		
			(5.8			
158		1.9			1.5	
159			5.2	2.5		
160		3.1	2.6			
161		2.0	2.2	3.7	4.0	6.3
162		3.0		2.1	3.9	3.1
163	3.8	4.6	3.2		4.5	7.5
164	2.7	1.8	(2.8	3.3		4.2
			(4.6			
165		2.9	0.9		3.5	

TABLE XXXIV (continued)

Number of Patient in Series	PREGNANCY (Weeks)			PUERPERIUM (Weeks)		
	Under 20	21 - 30	31-Delivery	Delivery-2	3 - 16	17+
166		3.2	2.3	3.0		2.0
167		2.1	3.1	3.1		
168	3.2		6.6	4.8	3.6	
169	2.1		2.7		3.3	
170		3.4	1.7		1.8	
171	2.1	0.9	3.7	3.5		0.8
MEAN (±S.E.)	3.02±0.31	3.26±0.41	3.48±0.35	3.38±0.49	3.28±0.42	3.49±0.6

TABLE XXXV - WOMEN WITH HEART DISEASE - VENOUS TONE (mm Hg/ml)

Number of Patient in Series	PREGNANCY (Weeks)			PUERPERIUM (Weeks)		
	Under 20	21 - 30	31-Delivery	Delivery-2	3 - 16	17+
172		(9.1 (2.0	1.3	0.8	1.8	
173			2.7	2.4		2.8
174			(3.6 (5.0	4.9	6.8	
175			2.5	2.4	2.7	
176		4.7	4.8	2.5	4.1	
177			2.9	2.2		
178			3.2		2.6	
MEAN (±S.E.)		5.27±2.2	3.25±0.44	2.53±0.54	3.60±0.88	2.8

DISCUSSION

These results show no consistent change in measured venous tone in pregnancy compared with after delivery or in the course of pregnancy.

This conclusion differs from the previous studies in pregnancy (McCausland et al. 1961, Goodrich and Wood 1964) referred to previously, and may reflect that different properties of venous behaviour are being measured by the different methods.

Since the technique used may be the fundamental factor in explaining this difference, an evaluation of the criticisms concerning the methods used in the present and previous studies is made. Brown and her colleagues (1963, 1966) have demonstrated variable rates of pressure rise in two forearm veins with sudden inflation of an occlusion cuff. The comparisons were made, either with one catheter centrifugally, directed, close to the venous occlusion cuff and the other centripetally directed from the wrist passing under the arterial occlusion cuff or with both vessels catheterised near the wrist. It seems probable that where a long catheterised segment exists between the site of pressure recording and venous occlusion, normal venous filling might be impeded either by the catheter itself or by closure of valves. It does not necessarily follow that a similar inaccuracy would exist with a small needle placed in a large vein within two to three inches of the venous occlusion cuff as used in the present study.

To establish this point, two needles were inserted centripetally into large forearm veins in five subjects. The distance of the needles

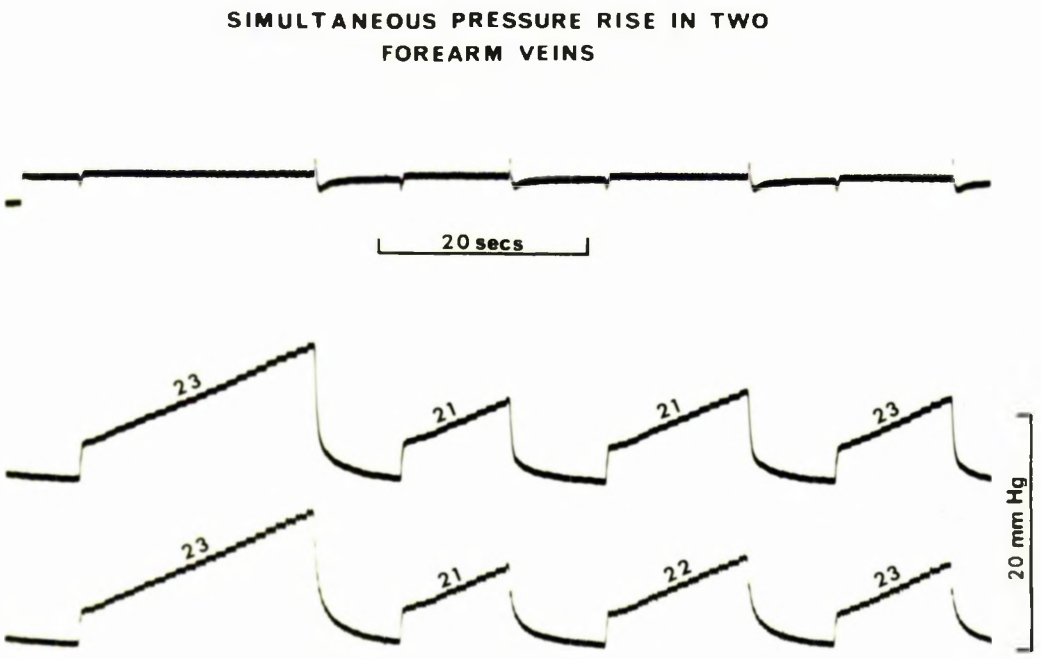


Fig. 40. The pressure rise is expressed in mm Hg / min. In this subject, one needle was in a vein in the lateral aspect of the antecubital fossa and the other 3 inches lower on the medial aspect of the forearm.

The top line on this record is a differential channel showing no difference between the slopes on each venous occlusion.

from each other and from a venous occlusion cuff just above the elbow varied depending on the availability of suitable segments. Provided the occluding cuff was positioned neither so close that a large artefact occurred nor so far away that there was delay before a rise in pressure occurred, linear increases in pressure of comparable magnitude occurred in 4 subjects (Fig. 40). In the remaining subject a sigmoid-shaped rise of varying shape occurred in both veins and it was assumed that there was a valve close to either or both needles. In the serial study in the patients in pregnancy the relative distance between the point of pressure recording and the venous occlusion cuff varied only slightly. Records showing non-linear pressure increments were discarded.

Despite the disadvantage of employing direct pressure measurements, it is possible that failure to do so, as in the previous studies in pregnancy (McCausland et al. 1961, Goodrich and Wood 1964) may lead to undetected errors. Thus, during investigations of the properties of the veins of the hand, Gauer and Thron (1962) found that arterial occlusion to the hand following low pressure congestion shows a protracted non-linear decrease of venous pressure despite the constant volume. They attributed this to "stress relaxation" of the veins. Since this pressure fall was regularly seen if the initial venous pressure exceeded 10 mm Hg, and since the steepness of fall depended on both the initial distension and time it cannot be assumed that, in the method used by McCausland and his co-workers (1961), the initial congesting pressure in the finger tip was maintained at the time the

stabilised volume was measured, nor that the increments in pressure were equal. Venous distensibility curves based on these measurements could therefore be associated with an unknown, variable error.

In the method used by Goodrich and Wood (1964), volume variation during an increment of effective venous cuff pressure of 30 mm Hg was measured, the veins being initially artificially collapsed by the use of external pressure. Since the base line was separately determined for each recording the actual cuff pressures must have varied between subjects. Even the effective venous pressure cannot necessarily be regarded as identical in all subjects since Bevegård and Shepherd (1965) found that when inflow increased, for example after exercise, actual venous pressure recordings were higher than during resting states even with a constant occlusion cuff pressure. Many studies have been made by Wood (1965) using this method and its general usefulness cannot be doubted. However, interpretation of relatively minor changes found in a group of different subjects studied once during or after pregnancy, as in the study reported (Goodrich and Wood 1964), must be made with caution, especially in the absence of direct pressure measurements.

The pressure-volume characteristics of the venous system in both isolated vessels in animals (Alexander, Edwards and Ankeney 1953) and in a human vascular bed (Gauer and Thron 1962) are complex and are further complicated in conscious human subjects by superimposed influences, such as emotion and thermal environment. Despite the studies in recent years, present understanding of the relationship of

pressure, flow and capacity does not permit quantitative interpretation of relatively minor changes.

This analysis of methodology in relation to the previous studies carried out in pregnancy, leads to the conclusion that, in view of the assumptions made, the findings were not sufficiently conclusive to justify the claim that there is a generalised reduction of venous tone in pregnancy. Allowance for the technical variations means that the results are not necessarily in conflict with those obtained in the present study.

An increase in forearm venous tone has been reported in heart failure (Sharpey-Schafer 1961). In the present study, no difference in venous tone was found in the pregnant patients with heart disease compared with healthy women. However, none of the patients with heart disease was in clinical heart failure at the time of study and the arm venous pressure was 6.6 mm Hg or lower.

CONCLUSIONS

From the present study and analysis of related studies, one may therefore conclude that it has not been possible to demonstrate an unequivocal reduction in the tone of the veins in pregnancy. Further investigation of an alteration in venous activity in pregnancy will require developments of methodology applicable to human pregnancy.

A generalised reduction in venous tone in pregnancy would, in any case, be difficult to reconcile with the undoubted increase in cardiac output in pregnancy. This increase must involve a corresponding

increase in venous return to the heart, which would become increasingly difficult to maintain if progressive venous dilatation occurred in the course of pregnancy.

Alterations in the ratio of pre to post-capillary resistance in pregnancy may have some bearing on the distribution and frequency of occurrence of oedema. Thus, where the arterioles dilate with no corresponding active dilatation in the venous system, the ratio of pre-capillary to post-capillary resistance falls. This relative change would lead to a greater extravasation of tissue fluid. The arteriolar vasodilatation in the hands and feet shown earlier in this thesis, could thus be a factor in the greater tendency of these structures to develop oedema. The wide variation in resting venous pressure in normal subjects and the varying extent of terminal limb segment vaso-dilatation in pregnancy could well be a factor in the variable degree of oedema in pregnancy. This is often of no pathological significance and has recently been shown to occur frequently in otherwise healthy women in pregnancy (Thomson, Hytten and Billewicz 1967).
It is, perhaps, worthy of comment that in the study on limb blood flow in multiple pregnancy (p. 76) one of the subjects (No. 54) with gross oedema of the feet and moderate oedema of the hands had marked arteriolar vasodilatation in these segments.

This mechanism may be involved in the greater frequency of oedema in toxaemia of pregnancy. However, the present study on the venous system was not extended to include patients with toxaemia and available knowledge does not, therefore, permit discussion of this at present.

SUMMARY

Measurement of venous tone in the forearm, in a group of healthy pregnant women and those with heart disease, both during and after pregnancy, has shown no reduction in venous tone in pregnancy.

FINAL SUMMARY AND CONCLUSIONS

A summary of the results of the different studies of this investigation is given at the end of the relevant section. A brief, integrated summary is provided here.

Analysis of the cardio-vascular response in the circulation during human pregnancy suggests that there is considerable variation in the extent of the circulatory change in different organs.

Investigation of the circulatory responses of the limbs, in the present study, has shown that there is no widespread change in the blood supply to skeletal muscle and to skin, but that there is progressive vasodilatation in the hands and to a lesser degree in the feet during normal pregnancy. Release of sympathetic vasoconstrictor tone is thought to be a likely mechanism of these changes.

The present study does not support the common belief that there is widespread venous dilatation in healthy women in pregnancy. It is suggested that increased filling of the veins in particular sites could be due entirely to an increase in local blood supply and, below the uterus, to obstruction of venous return to the heart.

Toxaemia of pregnancy and other hypertensive states in pregnancy are not associated with reduction in blood flow to the limbs and it is concluded that, if reduction in blood flow is associated with the rise in blood pressure, it must be occurring in only some vascular beds.

Since, in hypertensive pregnancy, the peripheral flow is unchanged, despite the increase in perfusion pressure, resistance

to blood flow must have increased. This increase in resistance has been shown to persist with vasodilatation induced by ischaemia and local exercise. An intrinsic change in the wall of the resistance vessels in hypertensive pregnancy has been postulated.

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APPENDIX

CLINICAL DETAILS OF PATIENTS STUDIED

Table A	-	Normotensive Women - Single Pregnancy
Table B	-	Normotensive Women - Multiple Pregnancy
Table C	-	Normotensive Women - Systemic Disorders
Table D	-	Normotensive Women - Obstetric Disorders
Table E	-	Women with Mild Toxaemia
Table F	-	Women with Severe Toxaemia
Table G	-	Women with Essential Hypertension
Table H	-	Women with Hypertension and Super-imposed Toxaemia
Table I	-	Women with Twins and Toxaemia
Table J	-	Normotensive Women with a History of Toxaemia
Table K	-	Healthy Women - Venous Tone Study
Table L	-	Women with Heart Disease - Venous Tone Study

TABLE A - NORMOTENSIVE WOMEN - SINGLE PREGNANCY

NO. IN SERIES	AGE	PARITY	MONTH OF DELIVERY	GESTATION AT DELIVERY (WEEKS)	LABOUR INDUCED	MODE OF DELIVERY	WEIGHT OF BABY (lbs.)	LACTATED
1	22	0 + 0	APRIL	39		L.S.C.S.	7. 2	-
2	25	0 + 0	FEB.	40		FORCEPS	9. 5	+
3	39	0 + 0	OCT.	40		L.S.C.S.	7. 3	+
4	27	0 + 0	NOV.	40		S.V.D.	6. 9	+
5	23	0 + 0	DEC.	39		S.V.D.	8. 1	+
6	23	0 + 0	SEPT.	41		S.V.D.	8. 5	+
7	28	1 + 0	FEB.	40		S.V.D.	7. 13	+
8*	33	0 + 0	MARCH	41	+	BREECH	6. 11	+
9	31	1 + 0	MAY	40		S.V.D.	6. 13	-
10	22	0 + 0	MAY	42	+	S.V.D.	7. 5	-
11	29	0 + 2	JULY	40		S.V.D.	7. 5	-
12	31	1 + 2	MARCH	38		S.V.D.	7. 2	-
13	27	1 + 0	APRIL	42		S.V.D.	7. 11	+
14	26	0 + 0	AUG.	41		S.V.D.	8. 1	+
15	21	0 + 0	APRIL	39		S.V.D.	5. 11	+
16	19	0 + 0	JUNE	41		S.V.D.	6. 9	+
17	28	0 + 0	DEC.	40		S.V.D.	7. 6	+
18*	21	0 + 0	NOV.	40		S.V.D.	6. 11	-
19*	30	1 + 0	SEPT.	41		FORCEPS	7. 4	-
20*	22	0 + 1	JUNE	41		S.V.D.	6. 14	+
21*	34	0 + 0	JUNE	42		S.V.D.	6. 8	+
22*	23	0 + 0	MAY	39		S.V.D.	6. 10	-
23	26	1 + 0	JULY	40		S.V.D.	6. 9	+
24	36	1 + 1	OCT.	39		S.V.D.	5. 9	+
25*	38	2 + 2	SEPT.	41		S.V.D.	7. 6	+
26*	31	0 + 0	DEC.	40		S.V.D.	7. 7	+
27	22	0 + 0	FEB.	40		S.V.D.	7. 5	+
28	27	1 + 1	FEB.	40		S.V.D.	6. 10	+
29	28	1 + 0	NOV.	41		S.V.D.	8. 5	+
30	25	0 + 0	DEC.	38		S.V.D.	4. 15	+
31	32	0 + 0	OCT.	43	+	FORCEPS	7. 9	+
32	24	0 + 0	MAY	39		S.V.D.	7. 15	+
33*	29	0 + 0	FEB.	39		S.V.D.	5. 14	+
34	27	1 + 0	JAN.	40		S.V.D.	7. 11	+
35	25	0 + 0	MAY	40		S.V.D.	6. 7	+
36	25	1 + 0	NOV.	40		S.V.D.	8. 7	+
37*	32	0 + 0	DEC.	40		S.V.D.	5. 15	+
38	28	0 + 0	JAN.	40		S.V.D.	6. 12	+
39	27	0 + 2	FEB.	40		S.V.D.	9. 8	+
40*	25	0 + 0	APRIL	42		S.V.D.	7. 7	+
41	26	1 + 0	OCT.	42		S.V.D.	8. 1	+

TABLE A (continued)

NO. IN SERIES	AGE	PARITY	MONTH OF DELIVERY	GESTATION AT DELIVERY (WEEKS)	LABOUR INDUCED	MODE OF DELIVERY	WEIGHT OF BABY (lbs.)	LACTATED
42	24	0 + 0	MAY	37		S.V.D.	5. 8	+
43	24	1 + 0	JUNE	40		S.V.D.	7. 3	+
44*	25	1 + 0	SEPT.	41		S.V.D.	8. 1	-
45	28	0 + 0	JAN.	40		S.V.D.	6. 5	+
46	38	4 + 0	AUG.	41	+	FORCEPS	9. 1	-
47	24	0 + 0	MAY	42	+	L.S.C.S.	8. 12	+
48	31	1 + 0	NOV.	41		S.V.D.	6. 7	+
49*	24	0 + 0	JULY	41		S.V.D.	6. 7	+
50	30	1 + 1	JULY	40		S.V.D.	8. 15	-
51*	25	0 + 0	AUG.	41		S.V.D.	7. 2	+
52*	20	0 + 0	AUG.	40		S.V.D.	7. 10	+

* Included in Arterielar Distensibility Study

S.V.D - Spontaneous Vertex Delivery

L.S.C.S. - Lower Segment Caesarean Section

TABLE B - NORMOTENSIVE WOMEN - MULTIPLE PREGNANCY

NO. IN SERIES	AGE	PARITY	MONTH OF DELIVERY	GESTATION AT DELIVERY (WEEKS)	LABOUR INDUCED	MODE OF DELIVERY	WEIGHT OF BABY (lbs.)	LACTATED
53*	29	0 + 0	MAY	40	+	FORCEPS FORCEPS	4. 12 5. 2	+
54*	29	0 + 0	JULY	40		L.S.C.S.	7. 5 8. 15	-
55*	25	1 + 0	NOV.	40	+	S.V.D. INT. VERS.	5. 0 7. 6	-
56*	25	0 + 0	MAY	38		FORCEPS FORCEPS	5. 4 3. 4	-
57*	29	0 + 0	FEB.	40		L.S.C.S.	5. 0 6. 1	+
58	35	1 + 0	OCT.	38		BREECH BREECH	5. 15 5. 5	+
59*	30	2 + 0	MAR.	39		FORCEPS FORCEPS	5. 11 5. 10	-
60	26	0 + 1	MAR.	36		S.V.D. S.V.D.	3. 12 5. 13	-
61*	22	0 + 0	APR.	38		S.V.D. S.V.D.	4. 13 5. 10	+
62*	22	0 + 0	AUG.	38		FORCEPS S.V.D.	5. 4	+
63*	21	0 + 0	JULY	39		L.S.C.S.	4. 0 6. 7	-
64	31	0 + 0	SEPT.	39		L.S.C.S.	7. 8 6. 0	+
65	27	0 + 2	JUNE	37		BREECH FORCEPS INT. VERS.	5. 0 5. 4 5. 6	+
66*	21	0 + 0	SEPT.	32		BREECH S.V.D. BREECH	3. 3 3. 6 3. 7	+

TABLE B (continued)

* Included in Arteriolar Distensibility Study

S.V.D. - Spontaneous Vertex Delivery

L.S.C.S. - Lower Segment Caesarean Section

INT.VERS. - Internal Version

TABLE C - NORMOTENSIVE WOMEN WITH SYSTEMIC DISORDERS

NO. IN SERIES	CONDITION	AGE	PARITY	MONTH OF DELIV-ERY	GEST-ATION AT DELIV-ERY	LABOUR INDUCED	MODE OF DELIVERY	WEIGHT OF BABY (lbs.)	LACTATED
67	Mitral Stenosis (Post-Valvotomy)	24	0 + 0	AUG.	40	-	S.V.D.	6. 9	-
68	Aortic Stenosis	26	2 + 1	AUG.	42	-	S.V.D.	8. 6	-
69	Diabetic	35	1 + 2	JAN.	37	Yes	L.S.C.S.	10. 0	-
70	Diabetic	22	1 + 0	OCT.	36	Yes	L.S.C.S.	9. 7	-
71	Spontaneous Hypo-glycaemia	31	1 + 0	MAR.	36	-	S.V.D.	6. 0	-
72	Post Adrenal-ectomy	33	0 + 0	OCT.	40	-	S.V.D.	7. 11	-

TABLE D - NORMOTENSIVE WOMEN WITH OBSTETRIC DISORDERS

NO. IN SERIES	CONDITION	AGE	PARITY	MONTH OF DELIV-ERY	GEST-ATION AT DELIV-ERY	LABOUR INDUCED	MODE OF DELIVERY	WEIGHT OF BABY (lbs.)	LACTATED
73	Dysmature Baby	25	0 + 0	MAR.	39	-	S.V.D.	3. 7	+
74	Revealed Accidental Haemorrhage	32	1 + 0	MAY	37	-	L.S.C.S.	6. 2	+
75	Twins - One I.U.D. at 34 weeks	22	0 + 0	FEB.	38	-	FORCEPS S.V.D.	5. 0 2. 14	+

S.V.D. - Spontaneous Vertex Delivery
L.S.C.S. - Lower Segment Caesarean Section
I.U.D. - Intra-uterine Death

TABLE E - WOMEN WITH MILD TOXAEMIA

NO. IN SERIES	AGE	PARITY	BLOOD PRESSURE AT BOOKING	MONTH OF DELIVERY	GESTATION AT DELIVERY	LABOUR INDUCED	MODE OF DELIVERY	WEIGHT OF BABY (lbs.)	LACT-ATED
76*	30	0 + 0	140/80	MARCH	39	Yes	S.V.D.	7. 12	-
77*	27	0 + 0	135/85	SEPT.	40	Yes	S.V.D.	7. 13	+
78*	19	0 + 0	120/70	MAY	40	Yes	S.V.D.	5. 6	+
79*	32	1 + 0	130/70	MARCH	39	Yes	S.V.D.	6. 8	-
80	27	0 + 0	130/80	JUNE	40	-	S.V.D.	7. 2	-
81*	21	0 + 0	120/70	APRIL	39	-	S.V.D.	7. 7	-
82*	34	1 + 0	120/75	JUNE	38	Yes	S.V.D.	6. 7	-
83*	25	0 + 0	115/80	JUNE	40	-	S.V.D.	6. 11	+
84*	27	0 + 0	100/70	AUG.	38	Yes	FORCEPS	6. 2	-
85*	34	0 + 0	130/70	SEPT.	38	Yes	S.V.D.	6. 13	+
86	23	1 + 0	115/80	MARCH	39	Yes	BREECH	5. 7	+
87*	25	0 + 0	110/70	MAY	40	Yes	S.V.D.	7. 13	+
88*	32	0 + 0	110/70	SEPT.	39	Yes	S.V.D.	5. 11	+
89*	29	0 + 0	150/75	JUNE	38	Yes	S.V.D.	5. 9	+
90*	31	1 + 0	130/70	MAY	39	Yes	S.V.D.	7. 3	+

* Included in Arterioler Distensibility Study

S.V.D. - Spontaneous Vertex Delivery

TABLE F - WOMEN WITH SEVERE TOXAEMIA

NO. IN SERIES	AGE	PARITY	BLOOD PRESSURE AT BOOKING	MONTH OF DELIVERY	GESTATION AT DELIVERY (WEEKS)	LABOUR INDUCED OR ELECTIVE SECTION	MODE OF DELIVERY	WEIGHT OF BABY (lbs.)	LACTATED	REMARKS
91*	20	0 + 0	125/80	AUG.	39	Yes	FORCEPS	7. 0	-	-
+92*	36	5 + 0	100/60	JAN.	35	I.A.H.S.	S.V.D.	3. 8	-	I.U.D. at 35 weeks
93*	36	1 + 0	140/80	MARCH	32	Yes	S.V.D.	3. 8	-	-
94*	21	0 + 0	110/70	MAY	37	Yes	S.V.D.	5. 15	Yes	-
95	26	0 + 0	105/60	MARCH	36	Yes	S.V.D.	2. 14	-	N.N.D. at 5 days
96*	20	0 + 0	150/85(at 34 weeks)	JUNE	37	Yes	S.V.D.	5. 3	-	-
97*	29	0 + 1	130/70	APRIL	39	Yes	S.V.D.	5. 15	Yes	Previous Hysterotomy for Toxaemia
98*	22	0 + 0	130/80	JULY	38	Yes	FORCEPS	6. 3	Yes	-
99*	18	0 + 0	130/100(at 30 weeks)	AUG.	36	Yes	S.V.D.	5. 3	-	-
100	18	0 + 0	150/100(at 36 weeks)	MARCH	37	Yes	S.V.D.	5. 5	-	-
101*	33	0 + 0	120/80	DEC.	29	Yes	L.S.C.S.	3. 3	-	N.N.D. at 2 days
102*	23	0 + 0	130/70	MARCH	39	Yes	S.V.D.	5. 1	-	-
103*	38	2 + 0	105/75	DEC.	37	Yes	S.V.D.	5. 13	Yes	-
104*	19	0 + 0	110/70	FEB.	39	Yes	S.V.D.	5. 8	Yes	-
105*	26	1 + 0	110/60	OCT.	33	Yes	L.S.C.S.	2. 10	-	-
+106	22	0 + 0	120/80	FEB.	39	Yes	FORCEPS	6. 8	Yes	-

* Included in Arteriolar Distensibility Series.
\+ Hypotensive drug used.
I.A.H.S. - Intra-amniotic hypertonic saline.

S.V.D. - Spontaneous Vertex Delivery.
L.S.C.S. - Lower Segment Caesarean Section.
N.N.D. - Neo-Natal Death.

TABLE G - WOMEN WITH ESSENTIAL HYPERTENSION

NO. IN SERIES	AGE	PARITY	BLOOD PRESSURE AT BOOKING	MONTH OF DELIVERY	GESTATION AT DELIVERY	HYPOTENSIVE DRUGS	LABOUR INDUCED OR C.S.	MODE OF DELIVERY	WEIGHT OF BABY (lbs.)	LACTATED
107*	27	2 + 0	140/100	JAN.	39	None	Yes	S.V.D.	6. 15	-
108*	25	0 + 0	140/90	JULY	39	None	-	S.V.D.	9. 7	Yes
109	40	1 + 0	160/100	MAY	40	None	-	L.S.C.S.	6. 1	-
110	29	0 + 3	150/90	OCT.	40	None	Yes	FORCEPS	7. 9	Yes
+111	35	1 + 0	140/90	NOV.	38	Methyl-dopa	Yes	ELECT.C.S	7. 12	-
112*	36	1 + 0	145/100	APRIL	38	None	Yes	S.V.D.	6. 7	-
+113*	23	0 + 0	140/100	FEB.	34	Methyl-dopa	Yes	S.V.D.	3. 13	-
114	25	1 + 0	160/100	NOV.	39	None	-	S.V.D.	6. 9	Yes
115	37	3 + 0	145/90	OCT.	39	None	-	S.V.D.	6. 1	-
116*	38	0 + 0	160/100	JULY	39	None	Yes	FORCEPS	7. 5	Yes
+117	28	0 + 0	140/100	MARCH	39	Decaserpyl	Yes	FORCEPS	6. 5	Yes
+118	37	0 + 0	160/110	NOV.	37	Decaserpyl+ Methyl-dopa	Yes	ELECT.C.S	5. 15	Yes
119*	41	1 + 0	140/90	FEB.	37	None	Yes	L.S.C.S.	6. 9	Yes
120*	40	4 + 0	200/110	APRIL	37	None	Yes	L.S.C.S.	7. 2	-
121*	39	0 + 1	145/90	FEB.	40	None	Yes	ELECT.C.S	7. 1	Yes
122	28	2 + 0	150/90	APRIL	40	None	Yes	S.V.D.	6. 14	Yes
+123*	30	0 + 2	150/95	JULY	37	Decaserpyl	Yes	ELECT.C.S	7. 3	Yes

* Included in Arteriolar Distensibility Study
\+ Hypotensive drug used
S.V.D. - Spontaneous Vertex Delivery
L.S.C.S. - Lower Segment Caesarean Section
Elect. C.S. - Elective Caesarean Section

TABLE H - PATIENTS WITH HYPERTENSION AND SUPERIMPOSED TOXAEMIA

NO. IN SERIES	AGE	PARITY	BLOOD PRESSURE AT BOOKING	MONTH OF DELIVERY	GESTATION AT DELIVERY	HYPOTENSIVE DRUGS	LABOUR INDUCED OR C.S.	MODE OF DELIVERY	WEIGHT OF BABY (lbs.)	LACTATED
+124*	29	1 + 0	150/90	OCT.	34	Decaserpyl+ Reserpine	Yes	L.S.C.S.	3. 6	-
125	27	1 + 0	150/90	DEC.	37	None	-	S.V.D.	5. 1	Yes
126*	41	1 + 0	145/100	JUNE	34	None	Yes	ELECT. S.C.	3. 0	-
+127*	28	1 + 0	150/90	APRIL	40	Reserpine	Yes	S.V.D.	7. 4	Yes

* Included in Arteriolar Distensibility Study
\+ Hypotensive drug used
S.V.D. - Spontaneous Vertex Delivery
L.S.C.S. - Lower Segment Caesarean Section
Elect.C.S.- Elective Caesarean Section

TABLE I - PATIENTS WITH TWINS AND TOXAEMIA

NO. IN SERIES	AGE	PARITY	MONTH OF DELIVERY	GESTATION AT DELIVERY (WEEKS)	LABOUR INDUCED	MODE OF DELIVERY	WEIGHT OF BABY (lbs.)	LACTATED
128*	24	0 + 0	DEC.	38	Yes	FORCEPS BREECH	6. 0 6. 2	-
129*	18	0 + 0	NOV.	38	Yes	L.S.C.S.	6. 1 5. 2	-

* Included in Arteriolar Distensibility Study

L.S.C.S. - Lower Segment Caesarean Section

TABLE J - NORMOTENSIVE WOMEN WITH A HISTORY OF TOXAEMIA

NO. IN SERIES	AGE	PARITY AND HISTORY	MONTH OF DELIVERY	GESTATION AT DELIVERY (WEEKS)	LABOUR INDUCED	MODE OF DELIVERY	WEIGHT OF BABY (lbs.)	LACTATED
130*	24	1 + 0 Severe Toxaemia	SEPT.	40	No	S.V.D.	7. 7	-
131*	26	1 + 0 Mild Toxaemia	OCT.	42	No	S.V.D.	8. 8	+
132*	26	1 + 0 Severe Toxaemia N.N.D.	JULY	40	No	S.V.D.	6. 9	+
133*	30	1 + 1 1. Hysterotomy for fulminating toxaemia. 2. Severe Toxaemia	JULY	41	No	S.V.D.	8. 15	+
134*		1 + 0 Eclampsia	SEPT.	40	Yes	S.V.D.	7. 9	+

* Included in Arteriolar Distensibility Study

S.V.D. - Spontaneous Vertex Delivery

N.N.D. - Neo-Natal Death

TABLE K - HEALTHY WOMEN - VENOUS TONE STUDY

NO. IN SERIES	AGE	PARITY	MONTH OF DELIVERY	GESTATION AT DELIVERY (WEEKS)	LABOUR INDUCED	MODE OF DELIVERY	WEIGHT OF BABY (lbs.)	LACTATED
135	37	0 + 1	AUG.	32	-	FORCEPS	3. 8	+
136	27	0 + 0	NOV.	40	-	S.V.D.	6. 9	+
137	29	2 + 0	MAY	41	-	FORCEPS	7. 10	+
138	29	0 + 0	MARCH	39	-	S.V.D.	6. 12	-
139	18	0 + 0	SEPT.	42	-	S.V.D.	8. 5	+
140	22	0 + 1	JUNE	41	-	S.V.D.	6. 14	+
141	19	0 + 0	MARCH	39	-	S.V.D.	7. 13	+
142	26	0 + 0	MARCH	39	-	FORCEPS	7. 10	+
143	23	0 + 0	JULY	35	-	S.V.D.	4. 12	+
144	27	0 + 0	JUNE	41	-	S.V.D.	7. 4	+
145	25	0 + 1	JULY	40	-	S.V.D.	8. 3	+
146	21	0 + 0	MAY	40	-	S.V.D.	7. 11	+
147	30	1 + 0	OCT.	41	Yes	S.V.D.	8. 3	-
148	22	0 + 0	SEPT.	40	-	S.V.D.	7. 2	+
149	26	0 + 0	OCT.	40	-	L.S.C.S.	7. 0	+
150	24	0 + 1	MAY	42	-	S.V.D.	8. 5	-
151	37	1 + 0	FEB.	39	-	S.V.D.	7. 6	-
152	37	0 + 0	MARCH	39	-	FORCEPS	7. 3	+
153	27	0 + 0	AUG.	40	-	V.E.	7. 10	+
154	30	0 + 1	MARCH	40	-	S.V.D.	6. 2	-
155	24	0 + 0	APRIL	37	-	S.V.D.	6. 13	+
156	24	0 + 0	JULY	41	-	S.V.D.	6. 6	+
157	27	0 + 0	AUG.	35	-	S.V.D.	5. 3	+
158	32	0 + 0	JUNE	40	-	BREECH	7. 6	+
159	27	0 + 0	MARCH	42	-	FORCEPS	9. 0	+
160	24	0 + 0	APRIL	40	-	S.V.D.	7. 4	+
161	33	0 + 0	AUG.	41	-	FORCEPS	7. 14	-
162	24	0 + 0	MAY	37	-	S.V.D.	5. 8	+
163	24	0 + 1	OCT.	42	-	FORCEPS	9. 0	+
164	30	0 + 0	OCT.	40	-	S.V.D.	8. 1	+
165	24	0 + 0	JUNE	39	-	S.V.D.	7. 5	+
166	37	0 + 0	MAY	38	-	S.V.D.	6. 0	+
167	23	0 + 0	MAY	40	-	S.V.D.	8. 0	+
168	27	0 + 1	SEPT.	42	-	L.S.C.S.	8. 1	+
169	34	0 + 0	SEPT.	40	-	FORCEPS	5. 13	+
170	25	1 + 0	JUNE	42	-	S.V.D.	7. 5	+
171	27	0 + 0	OCT.	41	-	S.V.D.	8. 0	+

S.V.D. - Spontaneous Vertex Delivery
L.S.C.S. - Lower Segment Caesarean Section

TABLE I - WOMEN WITH HEART DISEASE - VENOUS TONE STUDY

NO. IN SERIES	AGE	PARITY	NATURE OF LESION	MONTH OF DELIVERY	GESTATION AT DELIVERY (WEEKS)	MODE OF DELIVERY	WEIGHT OF BABY (lbs.)	LACTATED	REMARKS
172	29	4 + 0	MITRAL STENOSIS	NOV.	40	S.V.D.	7. 12	+	-
173	25	1 + 0	MITRAL STENOSIS	APRIL	44	S.V.D.	8. 7	+	-
174	20	0 + 0	MITRAL STENOSIS AND INCOMPETENCE	AUG.	41	FORCEPS	7. 15	-	P.P.H. Transfused 2 pints
175	26	2 + 1	AORTIC STENOSIS	AUG.	42	S.V.D.	8. 6	-	
176	22	0 + 0	MITRAL STENOSIS	DEC.	40	FORCEPS	5. 14	-	Valvotomy at 28 weeks of pregnancy
177	21	0 + 0	MITRAL STENOSIS	MARCH	40	S.V.D.	7. 4	-	Valvotomy 5 years before pregnancy
178	30	4 + 0	MITRAL STENOSIS	OCT.	41	S.V.D.	8. 2	-	Valvotomy at 21 weeks of pregnancy

S.V.D. - Spontaneous Vertex Delivery

P.P.H. - Post-partum Haemorrhage