# Section of Obstetrics and Gynæcology

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## DISCUSSION ON THE ÆTIOLOGY OF PRE-ECLAMPSIA

**Professor J. C. McClure Browne:**

*Placental Ischæmia is not an Ætiological Factor in Pre-eclamptic Toxæmia*

No two speakers on the subject of pre-eclamptic toxæmia will present the same points of view, because there are as many theories on this subject as there are obstetricians.

My interest in pre-eclamptic toxæmia and its ætiology is, I think, clearly an inherited one, and obviously it must be due to some hitherto undescribed dominant gene. Then in 1946 I was fortunate enough to come under the influence, first at Hammersmith and later in Edinburgh, of Professor Robert Kellar, who in his own inimitable way goaded me into taking a more active interest in this particular problem. About that time, too, the work of Beker (1948) and of Bastiaanse and Mastboom (1949) revived attention on the placenta as the supposed starting-point of the chain of events which culminates in eclampsia. As far back as 1914, Professor James Young—my predecessor at Hammersmith Hospital—had postulated that the red infarct which could be, and still can be, demonstrated in cases of eclampsia was the site of origin of chemical substances which initiated the whole syndrome. Ernest Page (Ogden *et al.*, 1940), too, had shown that partial occlusion of the aorta in the pregnant bitch resulted in a rise in systemic pressure. From these observations, and others, arose the idea that placental ischæmia existed in pre-eclamptic toxæmia, and, as with so many matters in obstetrics, once it had been postulated, it became apparently accepted as a fact, and on this supposed fact new theories of the ætiology of pre-eclamptic toxæmia were put forward.

If one accepts that placental ischæmia will indeed cause a rise in systemic blood pressure, then it is logical to suppose that pre-eclamptic toxæmia will develop in conditions where the pregnant uterus is subject to over-distension; conditions such as hydramnios, twins and, in some cases, in the primigravida. Professor K. Franklin and Mr. Sophian have shown that distension of the pregnant rabbit uterus will cause a renal cortical ischæmia which could be held to account for the occurrence of albuminuria. Recently, however, McGaughey *et al.* (1956) in experiments on the dog have failed to show that a specific utero-renal reflex exists.

Up till 1948, though there was evidence to suggest that placental ischæmia might have an important role to play in the ætiology of pre-eclamptic toxaemia, nobody had shown that such a condition actually existed, and it seemed to me vital to prove or disprove this. To do this Veall and I considered that it was important that the placenta should be studied *in situ* before the fœtus was delivered, and indeed before the uterus was opened. The first problem was to find the placenta under these conditions, and for this reason we developed a method of locating it using tracer doses of radio-active sodium (Browne, 1951). The method (Browne and Veall, 1953), though established purely for this experimental purpose, has important clinical applications in the exclusion of placenta prævia as a possible cause of antepartum hæmorrhage, and is in general use to-day at Hammersmith for that purpose.

In cases where we found that the placenta was situated anteriorly it was possible to inject a tracer dose of $^{24}Na$ into the chorio-decidual space, and to record the time taken for it to be cleared by the maternal placental circulation In the normal case—that is to say the woman without pre-eclamptic toxæmia or hypertension—between 38 and 40 weeks the mean half-period for clearance was 21 seconds. In cases with pre-eclampsia the mean half-period was 65 seconds, more than three times as long, showing clearly that in pre-eclampsia a true placental ischæmia existed. However, in cases of essential hypertension, even mild cases, where the hypertension had antedated the pregnancy, the same degree of ischæmia was found. We concluded therefore that the placental ischæmia was the result and not the cause of the hypertension which is one of the cardinal features of pre-eclamptic toxæmia. We were astounded at the marked reduction in maternal placental blood-flow that occurred when hypertension was present, and at first refused to accept it as valid. However, careful review of our methods and results showed that we should indeed accept it. Subsequently, Morris *et al.* (1955) at University College Hospital adapted our method to study the clearance of radio-active sodium from uterine muscle, and showed that there, too, the same reduction in blood-flow as evidenced by prolongation of clearance time existed. Walker and Turnbull (1953), working on the other side of the placental membrane, found that in these conditions there was evidence of fœtal anoxia, in that the concentration of hæmoglobin

in the fœtal blood was raised. Neither Morris nor I found any diminution of tissue clearance in striated muscle.

The existence of this placental ischæmia in cases of hypertension, whether essential or pre-eclamptic in origin, explained many things. For example, it explained why the baby tends to be small in cases of essential hypertension and the serious significance of hypertension in association with post-maturity in which placental insufficiency is also a feature (Browne, 1954). It explained, too, many of these cases of intra-uterine death in the last few weeks of pregnancy, when only a mild hypertension was present.

This clear evidence, therefore, that hypertension causes placental ischæmia, suggests that the uterine tension theory for the origin of pre-eclampsia is wrong. We are told by the exponents of this theory that the tension of the primigravid uterus, or the presence of twins, or hydramnios, conditions frequently associated with pre-eclamptic toxæmia, produces a placental ischæmia and if the intra-uterine tension be reduced—for example, by rupturing the membranes—then the ischæmia is diminished and the toxæmia is immediately improved. But this certainly is not my experience in clinical obstetrics, and I am sure we would all agree that there are many instances of serious deterioration in cases of pre-eclamptic toxæmia after surgical induction has been performed, so that we are compelled on occasion to perform Caesarean section in this particular type of case because of imminent eclampsia.

## REFERENCES


BASTIAANSE, M. A. VAN B., and MASTBOOM, J. L. (1949) *Ned. Tijdschr. Geneesk.*, **93**, 2609.
BEKER, J. C. (1948) *J. Obstet. Gynaec., Brit. Emp.*, **55**, 756.
BROWNE, J. C. McC. (1951) *Proc. R. Soc. Med.*, **44**, 715.
—— (1954) La Prophylaxie en Gynécologie et Obstétrique. Geneva; p. 1015.
——, and VEALL, N. (1953) *J. Obstet. Gynaec., Brit. Emp.*, **60**, 142.
MORRIS, N., OSBORN, S. B., WRIGHT, H. P. (1955) *Lancet, i*, 323.
MCGAUGHEY, H. S., WELLER, H., and ANSLOW, W. P. (1956) *Amer. J. Obstet. Gynec.*, **72**, 589.
OGDEN, E., HILDEBRAND, G. J., and PAGE, E. W. (1940) *Proc. Soc. exp. Biol., N.Y.*, **43**, 49.
WALKER, J., and TURNBULL, E. P. M. (1953) *Lancet, ii*, 312.
YOUNG, J. (1914) *Proc. R. Soc. Med.*, **7**, Sect. Obstet., p. 307.


**Mr. Norman Morris:**

The pioneer work of Professor McClure Browne stimulated Dr. Helen Payling Wright and myself to investigate the clearance rate of $^{24}Na$ from the myometrium. Initially we selected mothers at rest in hospital between 30 weeks and term. A point was chosen on the abdominal wall about 4 cm. below and lateral to the umbilicus. This was infiltrated with between 1 and 2 c.c. of 1% lignocaine. The injection needle was then introduced through this area into the myometrium and 0·3–0·4 ml. of $^{24}Na$ with an activity of between 5 and 10 $\mu$c. was injected (*see* Fig. 1). A Geiger counter was then arranged over this site and the rate of clearance of the $^{24}Na$ recorded. After correcting our results for the rising background they were then expressed in terms of the time taken for the counting rate to reach half value (Fig. 2). These figures clearly show a reduction in clearance rate and therefore presumably of myometrial blood flow in relation to pre-eclampsia.

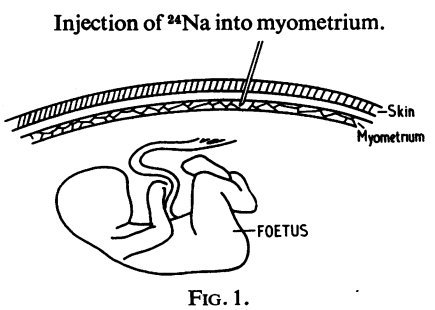


FIG. 1.

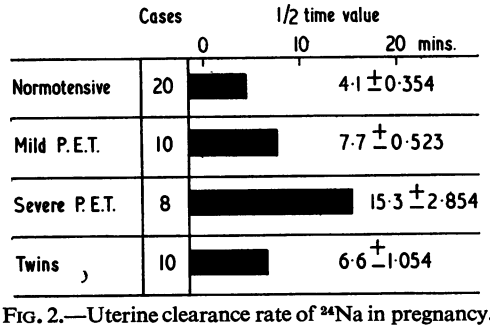


FIG. 2.—Uterine clearance rate of $^{24}Na$ in pregnancy.

Our series was then extended to some 90 cases. In a few we measured the clearance rate after lowering the blood pressure with protoveratrine and the results are shown in Fig. 3. Lowering the blood pressure appeared to improve the clearance rate.

We then investigated the effect of exercise upon the clearance rate of Na from both the myometrium and the anterior belly of the quadriceps. For this we devised an Exercycle. With the patient at rest an initial clearance reading from an injection into both the uterus and the quadriceps was obtained in a similar way to that already described. She

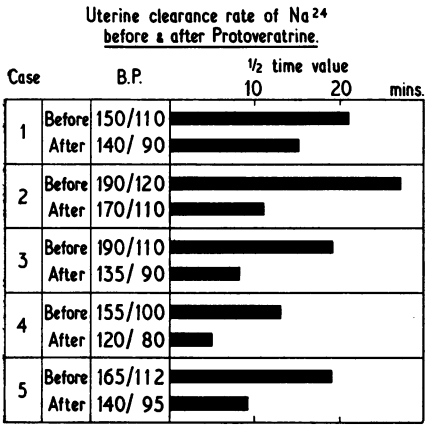


FIG. 3.

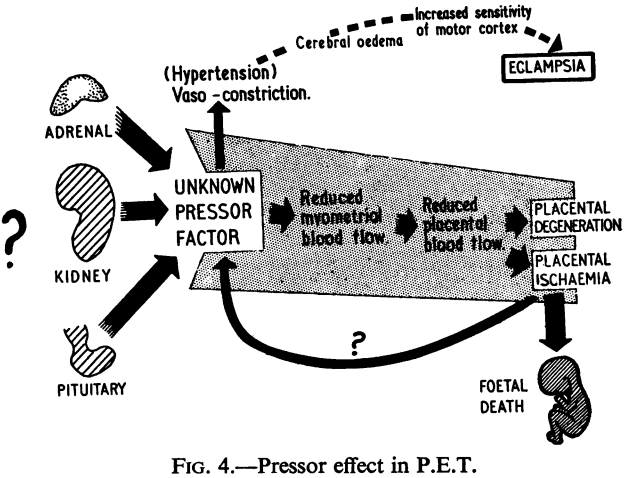


FIG. 4.—Pressor effect in P.E.T.

was then encouraged to use the apparatus; after she had achieved a steady pace for some 5 minutes, she stopped for a few moments just long enough for us to give an injection into the uterus and quadriceps. After this she resumed her cycling for a further 5 minutes. At this point she stopped and was encouraged to relax as much as possible. The results were as follows:

In both groups there was a significant rise in diastolic pressure during exercise. In the 5 minutes following the pressure fell rapidly towards the resting level.

| | Resting | During exercise | After exercise |
|---|---|---|---|
| Normals .. | 73·3 ± 1·75 | 85·5 ± 2·22 | 75·8 ± 2·31 |
| Pre-eclamptics .. | 93·3 ± 1·71 | 98·9 ± 2·53 | 91·4 ± 2·45 |

In both groups there was a statistically significant decrease in uterine clearance rate during exercise. This quickly returned to normal within 5 minutes when exercise was stopped.

Uterine clearance rate: Time to half value in minutes.

| | Resting | During exercise | After exercise |
|---|---|---|---|
| Normals .. | 4·07 ± 0·27 | 5·43 ± 0·42 | 3·07 ± 0·43 |
| Pre-eclamptics .. | 7·17 ± 0·22 | 8·75 ± 0·52 | 6·25 ± 0·53 |

These results therefore suggest that during exercise there is a reduction in blood flow to the uterus with a quick return after this is stopped. Furthermore it seems probable that this reduction in uterine blood flow is the result of a generalized splanchnic vaso-constriction since in the non-pregnant exercise also reduces the renal blood flow. The actual extent of reduction is possibly governed by many other considerations such as height, weight, skeletal development and the general state of bodily fitness.

It may be of value to consider the possible clinical significance of these findings. It is well established that rest usually helps to prevent deterioration in a case of pre-eclampsia; physical activity appears to have the reverse effect.

The origin of the pressor mechanism is unknown. Mr. Sophian thinks it largely originates from the kidney, others think it may come from the placenta while still others believe it may arise in the adrenal or pituitary. Whatever its origin, we would probably agree that its effect on the uterus and placenta is as indicated in Fig. 4. It can be seen that exercise by intensifying the vaso-constriction will also temporarily exacerbate these changes.

Since physical activity produces a subsequent hypertensive exacerbation of some duration it would appear that the increased splanchnic vaso-constriction provoked during exercise may also have the effect of stimulating or perpetuating the production of the pressor factor from whatever viscera this may arise.

In this way a vicious cycle is established. The blood pressure rises and eclampsia becomes more imminent. The uterine blood flow is progressively reduced. The changes occurring in the placenta are illustrated in Fig. 5. The placental blood flow is impaired and trophoblastic anoxæmia results. This, in turn, may result in irreversible trophoblastic degeneration and infarct formation. These changes may be associated with an intrinsic failure of placental development which sometimes seems to be a related factor in severe early pre-eclampsia.

As term is approached there is a natural reduction in placental function, sometimes referred to as "senility".

As a result of all these changes there is a progressive reduction in placental function and intra-uterine death of the foetus may occur. Rest can only partially reverse this sequence of events and, clearly, to be effective, it must be instituted at a very early stage.

Fig. 6 illustrates the ill-defined frontier between the normal patient and the one with

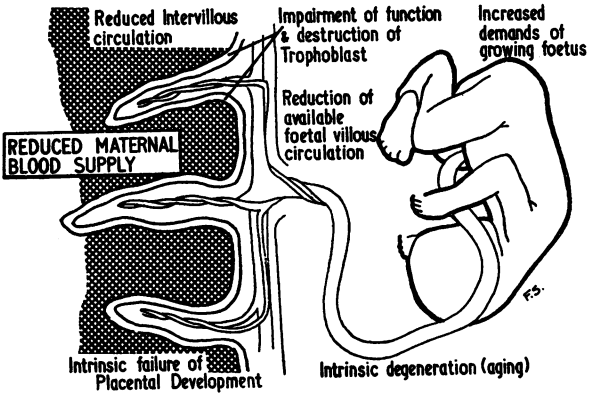


FIG. 5.—Placental changes in P.E.T.

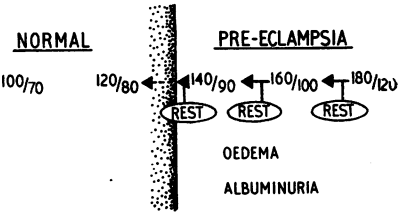


FIG. 6.—The effect of rest on the incidence and severity of P.E.T.

pre-eclampsia. Many of us do not agree regarding the upper limit of the normal blood pressure and we confine our attention to those patients who show indisputable evidence of pre-eclampsia, such as hypertension, œdema, and albuminuria. Our results are good, but many women do progress to moderate or even severe pre-eclampsia before we see them.

I believe that *all* primigravidæ and any other patient thought to be particularly susceptible to pre-eclampsia should be advised to rest as much as possible from 30 weeks onwards. In all probability this measure would completely alter the pattern of severity of pre-eclampsia. The mild cases would occur later, or never at all; the moderate would become mild, and the severe, moderate. In turn the perinatal mortality from this condition should be much reduced.

**Mr. John Sophian:** *The Cause of Pregnancy Toxæmia*

If patients with incipient or pre-existing hypertension are excluded toxæmia is *never* met with outside primigravidity, hydramnios, concealed accidental hæmorrhage, hydatidiform mole, or multiple pregnancy.

Since "essential" hypertension can possibly occur as a result of a renal mechanism [1], and since renal ischæmia can be held to explain the œdema, hypertension and albuminuria which characterize the toxæmic state [2]—signs entirely similar to those of acute glomerular nephritis, an undoubted renal disease [41]—it is reasonable to infer that a renal ischæmic change occurs in pre-eclampsia. This condition is associated with an increased resistance to stretch of the uterine muscle and such a resistance could be evoked by uterine over-distension; or even normal distension of the primigravid uterus. The utero-renal reflex demonstrated by Franklin and Sophian [3] has shown that by provoking resistance in the rabbit's uterus (by fluid distension) a stimulus is produced causing renal cortical ischæmia. Evidence has thus been produced to correlate these renal changes with toxæmia [4]; further, all grades of renal ischæmic change, and cortical necrosis have been produced by renal nerve stimulation [5], which suggests that anuria can result from a reflex response. Evidence of a utero-renal reflex is provided by the over-distension of the uterus in concealed accidental hæmorrhage causing anuria due to renal cortical ischæmia. It has been shown that removal of the distension-stimulus by rupture of the membranes and interruption of the suggested nervous reflex by splanchnic block [6 and 7] is sufficient to overcome incipient or early anuria. Correlation of the severe cortical ischæmia of anuria with the renal state underlying pre-eclampsia was shown when intravenous saline, mistakenly administered as a therapeutic measure to an anuric, precipitated œdema, hypertension and fits [8]. Albuminuria is always detectable in the earlier oliguric phase and when an excess of salt and water exists in the presence of renal ischæmia all signs of toxæmia are evoked. Pre-eclampsia and eclampsia may also be produced when this sequence is reversed, salt and water retention being preliminarily affected by giving D.O.C.A. and salt, followed by renin [9].

In the pre-eclamptic process there is a great deal of evidence to show that renal ischæmia

is continuing as pregnancy advances, evidence that is derived from the reduced glomerular filtration rate and renal plasma flow figures [10] and from renal biopsies [11]. The signs can also be construed as those resulting from renal ischæmia [12]. It is suggested therefore that the *continuing* ischæmia of the kidney is responsible for the signs of pre-eclampsia. *Sudden* renal shut-down, as evidenced by the development of anuria, has a possible counterpart in the suspension of renal function in the salmon when it changes its river habitat for the sea; and it can be shown that this is entirely due to the presence of salt in the new environment [13]. It should be noted also that the kidney is more prone to an "anuric" shut-down if the liver is damaged [14], and as a corollary, renal damage of an ischæmic type can result from compression of the porta hepatis [15]. The supervention of fits, coincident with severe exacerbation of hypertension, has been seen following prolonged clamping of the remaining renal pedicle, after unilateral nephrectomy; cerebral vascular spasm accompanies this manifestation. Further, these experimental animals, who have been kept on saline, can occasionally develop severe œdema, thus demonstrating the association of œdema, hypertension and fits with ischæmia of the kidney [16]. In the causation of fits, changes in the electrolyte concentration of the plasma have been shown to be responsible [17]. Sodium and chloride concentration of the plasma can therefore be responsible both for a renal shut-down, as in the salmon, and for the production of fits, while salt is necessary for the production of hypertension [18]. Renal ischæmia can cause the retention of salt and water [42] and a 1% reduction of the glomerular filtration rate (G.F.R.) can account for the retention of 10 grams sodium daily—a not inconsiderable amount when spread over the later months of a toxæmic pregnancy when G.F.R. is markedly reduced. Recent work in the experimental animal has demonstrated a reduction of one-third in the G.F.R. during the early periods of uterine distension [19]. Nephron dissections, which help to differentiate purely ischæmic lesions from those in which poisons have been active, clearly indicate that the tubular damage is due to ischæmia in the anuria following eclampsia [20]. All this evidence suggests the presence of renal ischæmia in pre-eclampsia which by producing salt and water retention can be responsible for hypertension, fits and even anuria. Alternatively, the principal effect of renal ischæmia may be directly upon the vascular system, enhancing hypertension and evoking encephalopathy. It has been shown in nephritis that reducing the renal blood flow increases the escape of protein through the glomerular filter by slowing the stream, suggesting that renal ischæmia produces the albuminuria as well [21]. It follows that every sign and complication of toxæmia can be explained by renal ischæmia. Corticoids [22], which are in the main responsible for the shifts of retained water and electrolytes in the body compartments are of secondary importance.

Evidence that the uterine stimulus originates in the resistance to stretch of the myometrium is both direct and indirect. Uterine tone has been shown to be raised in hydramnios [23], in toxæmic pregnancy [24], in concealed accidental hæmorrhage [25] and also in hydatidiform mole in which Acosta-Sison [26] has drawn attention to the association of the height of the uterus with the severity of the toxæmia, an implication of increased regression also present in primiparity indicating increased myometrial tension [37]. Apart from this direct evidence, puncture of the membranes in pre-eclampsia [27] and oliguria [28] is associated with clinical improvement before labour commences, while introduction of a hydrostatic bag for purposes of induction in toxæmia has been observed at least on one occasion to precipitate anuria. It should be added that interrupting the arc of the utero-renal reflex by caudal analgesia has great therapeutic value [29], as has destruction of the nervous pathways [38]. It has been shown, that increased tension of the uterine wall causes a reduced circulation through the myometrium [30] while a noticeably reduced myometrial circulation has been found constantly and continuously in pre-eclampsia [31]. This circulation can also be diminished by exercise [12]. On one occasion in toxæmic pregnancy considerable augmentation of the blood flow through the uterine wall and amelioration of the pre-eclamptic signs were apparent on the death of the fœtus [32]. Presumably this was due to its crumpling, resulting in a reduction of the stretch factor with corresponding diminution of the utero-renal reflex. Prolonged contraction of the uterus during labour has on one occasion been found to coincide with the onset of toxæmia [33]. The adenosine content of the blood in toxæmia, indirect evidence of a heightened uterine tone, has been found to be much higher than in normal pregnancy [34].

Toxins originating from the fœtus or the placenta cannot be responsible for the ætiology, since amelioration of toxæmia results on the intra-uterine death of the fœtus, although it is still retained *in utero*. Such toxæmia can recrudesce at labour when the death of the fœtus and placenta exclude the renewed manufacture of such hypothetical substances [4]. Nephron dissections of the kidney of patients with eclamptic anuria do not show any toxic effect on the tubules [20]. Neither is it reasonable to assume that toxin production is exclusive to first pregnancies alone; indeed no toxin has yet been found.

Examination of the hypothesis that hormones are responsible for pre-eclamptic signs suggests that such substances play no primary part in production [35]. An antigen reaction can be excluded, as its incidence should become more pronounced in later pregnancies, whereas toxæmia is a disease of the primigravid. Dietetic theories fail to appreciate the effect of salt which aggravates the condition.

Certain criticisms have been levelled against the thesis put forward here viz.:

(1) It cannot explain postpartum eclampsia. But Franklin has found renal ischæmia particularly marked during labour and coinciding with the postpartum contractions of the uterus.

(2) It has failed to produce toxæmia experimentally. This work was carried out with rabbits and the rabbit's uterus cannot resist stretch for a period long enough to allow pre-eclampsia to develop; neither has the animal suitable suprarenals, a fact indicated by the D.O.C.A. priming necessary to provoke eclampsia [9].

(3) A denial of the existence of the "dual" [Trueta, 39] circulation in the kidney on which the thesis is based. This criticism originated because current biochemical interpretations of renal hæmodynamics were only valid for a single renal circulation. However, Pappenheimer [36] claims that a dual circulation must be postulated to explain the filtration fraction and the less than 100% extraction ratio that prevails.

It is again postulated that the ætiology of toxæmia is to be found in the resistance of the myometrium to stretch provoking renal ischæmia. This, if pre-existent in essential hypertension or brought about by the utero-renal reflex or exercise [40] explains the reduced uterine blood flow it effects.

## REFERENCES


1 WILSON, C., and LEDINGHAM, J. M. (1956) *Brit. med. J.*, ii, 1236.
2 SOPHIAN, J. (1953) Toxæmias of Pregnancy. London.
3 FRANKLIN, K. J., and WINSTONE, N. E. (1955) *J. Obstet. Gynaec. Brit. Emp.*, **62**, 29.
4 SOPHIAN, J. (1955) *J. Obstet. Gynaec. Brit. Emp.*, **62**, 37.
5 FRANKLIN, K. J. (1950) *Proc. R. Soc. Med.*, **43**, 467.
6 FEENEY, J. K. (1953) *J. Irish Med. Ass.*, **32**, 36.
7 SOPHIAN, J. (1957) *Lancet*, i, 1044.
8 DIECKMANN, W. J. (1952) Toxæmias of Pregnancy. 2nd Ed., London; p. 347.
9 GAUNT, R., and RENZI, A. A. (1953) *Amer. J. Physiol.*, **175**, 313.
10 BUCHT, H., and WERKÖL, L. (1953) *J. Obstet. Gynaec. Brit. Emp.*, **60**, 157.
11 POLLAK, V. E., PIRANI, C. L., KARK, R. M., MUEHRCKE, R. C., FREDA, V. C., and NETTLES, J. B. (1956) *Lancet*, ii, 59.
12 SOPHIAN, J. (1957) *Lancet*, i, 48.
13 SMITH, H. W. (1943) Lectures on the Kidney. Lawrence, Kansas.
14 FAJERS, C.-M. (1956) *Acta path. microbiol. scand.*, **39**, 235.
15 CROWSON, C. N., and MORE, R. H. (1956) *Arch. Path.*, **60**, 73.
16 BYROM, F. B. (1954) *Lancet*, ii, 201.
17 HAMBURGER, J. C., and MATHÉ, G. (1952) Physiologie normale et pathologique du métabolisme de l'eau. Paris.
18 LEDINGHAM, J. M. (1957) *Brit. med. Bull.*, **13**, 33.
19 MCGAUGHEY, H. S., WELLER, H., and ANSLOW, W. P. (1956) *Amer. J. Obstet. Gynec.*, **72**, 589.
20 OLIVER, J., MAC DOWELL, M., and TRACY, A. (1951) *J. clin. Invest.*, **30**, 1305.
21 LATHEM, W. (1956) *J. clin. Invest.*, **35**, ii, 1277.
22 VENNING, E. H., SINGER, B., and SIMPSON, G. A. (1954) *Amer. J. Obstet. Gynec.*, **67**, 542.
23 CALDERO-BARCIA, C., POSE, S. V., and ALVAREZ, H. (1957) *Amer. J. Obstet. Gynec.*, **73**, 1238.
24 PARVIAINEN, S., LANKINEN, S., and SOIVA, K. (1951) *Gynæcologia*, **132**, 19.
25 SMYTH, C. N. (1957) *Lancet*, i, 933.
26 ACOSTA-SISON, H. (1956) *Amer. J. Obstet. Gynec.*, **71**, 1279.
27 VARTAN, C. K. (1957) Personal Communication; and many other authorities.
28 NIXON, W. C. W. (1954) Personal Communication.
29 HINGSON, R. A. (1947) *Curr. Res. Anesth. Analg.*, **26**, 177, 238.
30 REYNOLDS, S. R. M. (1950) Physiology of the Uterus. 2nd Ed. New York.
31 MORRIS, N., and WRIGHT, H. PAYLING (1956) *Lancet*, ii, 481.
32 —— (1955) Personal Communication.
33 NIXON, W. C. W. (1956) Personal Communication.
34 GREEN, H. N., HOPEWELL, J. D., and THRELFALL, C. J. (1951) *Brit. med. J.*, ii, 571.
35 SOPHIAN, J. (1956) *Amer. J. Obstet. Gynec.*, **72**, 693.
36 PAPPENHEIMER, J. R., and KINTER, W. B. (1956) *Amer. J. Physiol.*, **185**, 377.
37 REYNOLDS, S. R. M., and BAKER, J. T. (1951) *Contr. Embryol. Carnegie Inst.*, **34**, 75.
38 THEOBALD, G. W. (1953) *Brit. med. J.*, i, 422.
39 TRUETA, J., BARCLAY, A. E., DANIEL, P. M., FRANKLIN, K. J., and PRICHARD, M. M. L. (1947) Studies of the Renal Circulation. Oxford.
40 BRADLEY, S. E. (1950) *Amer. J. Med.*, **9**, 772.
41 SOPHIAN, J. (1956) In: The British Encyclopædia of Medical Practice, Medical Progress. London; p. 121.
42 WHITE, H. L. (1950) In: 2nd Conference on Renal Function. Josiah Macy Jr. Foundation. New York; p. 127.