more effective as contraceptives at the selected dosage. It may well be that the mode of action of low dosage progestogens in controlling fertility is less dependent on changes in cervical mucus and operates predominantly through other mechanisms.⁶⁻⁷ It is also possible that the time factor and duration of action may play a more significant part when lower dosages are employed. Norethisterone, norgestrol, and chlormadinone were very much more effective, although the pregnancy rates were considerably higher than reported by other observers.⁸⁻¹⁰ Dr. Mears is of the opinion that the majority of pregnancies occur in the early cycles, and that her figures for this study are therefore compatible statistically with the data published elsewhere.

In this connexion I would like to present some preliminary data on a personal study with norgestrol in a dosage of 0.05 mg. daily for fertility control. Information has been obtained over 800 cycles of medication. There have been no pregnancies. Four women have withdrawn from the study; three in order to enlarge their families and one on my instructions owing to irregular and persistent heavy bleeding. The three women who wished to become pregnant all conceived within two months of stopping norgestrol. The dosage instructions were somewhat different from those usually employed and may be of some interest.

The patients visited the clinic any day of their cycle and following examination were told that the tablets must be taken daily and may be relied on from the first day, but some four hours should be allowed from the time of taking the tablet and coital activity restricted to 14 hours from the time of medication. With continued use this restriction is gradually relaxed. It is pointed out that day 1 bears no relation to the cycle day, and some 20% of patients started the medication around the time of midcycle. The rationale is based on some previous studies using megesterol acetate as a pre-coital pill. The mean parity of the women in the study is over two.

The precise mechanism of action of mini-dose progestogens is not known, but whether it be effects on cervical mucus, alterations in ovum transport, endometrial nidation, changes in corpus luteum function,¹¹ or progesterone metabolism, or interference with sperm capacitation, certainly it would appear that some antifertility effect takes place rapidly. The onset of action and duration of effect may be fairly critical during the early months of medication and may account for a number of pregnancies observed by some investigators in the early cycles of treatment.—I am, etc.,

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Fibrin Degradation Products

SIR,—In their recent article Dr. John Bonnar and others (19 July, p. 137) found that the levels of fibrin/fibrinogen degradation products (F.D.P.) remained unchanged during normal pregnancy. Previously Woodfield *et al.*¹ had reported a progressive rise during the second and third trimester. In my opinion, this reported difference may be due to the anti-human fibrinogen serum used in the haemagglutination inhibition immuno-assay (H.I.I.) technique² which they utilized to measure F.D.P.

Both groups of authors used a Hoechst Pharmaceuticals anti-serum to fibrinogen, produced in rabbits, but as the two papers were published some six months apart it seems unlikely that they had both used the same batch of anti-serum. Of the many peptide fragments produced by the degradation of fibrinogen by plasmin, only two named fragments, D and E, react with an anti-fibrinogen serum.³ Nussenzweig *et al.*⁴ showed that different anti-fibrinogen sera prepared in rabbits against the same human fibrinogen contained different amounts of anti-fragment D and anti-fragment E. As the H.I.I. method of estimating F.D.P. measures the "sum" of levels of fragments D and E, it is not surprising that different antisera give different values for F.D.P. in a serum from a given patient.

The difference between Bonnar's and Woodfield's results could be explained thus: (a) a rise of either D or E occurred, but Bonnar's anti-serum contained only a small amount of antibodies reacting with this fragment and hence his group failed to show a rise of F.D.P. as pregnancy progressed, or (b) a rise of either D or E occurred, but the levels of the other fragment fell, and as Woodfield's anti-serum contained only a small proportion of antibodies to the fragment whose level was falling, their estimation of total F.D.P. showed a rise.

With the availability of a commercial kit for estimating F.D.P. (Burroughs Wellcome) it is essential that the proportion of anti-fragment-D and anti-fragment E should remain constant from one batch of anti-serum to the next. If this is not ensured, we shall have a situation exactly analogous to that which, until recently, prevailed in the field of anticoagulant control, where the results of the one-stage prothrombin time performed in different laboratories were by no means comparable.—I am, etc.,

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Aetiology of Pre-eclampsia

SIR,—In reply to Mr. G. J. Sophian (26 July, p. 241) I would like to point out that an intravascular coagulation theory is the only way of explaining the immuno-fibrin

that is demonstrated in the swollen endothelial cells. Vassalli¹ has shown by infusing rabbits with thromboplastin that a whole spectrum of changes can be produced from "endotheliosis," the equivalent of pre-eclampsia, to frank intraglomerular thrombi as in eclampsia. Similar findings in rats were found by Margaretten *et al.*²

I cannot agree that this "endotheliosis" is a feature of ischaemia *per se*: this is a reaction of the endothelium to the presence of fibrin, antigen-antibody complexes, and other macromolecules. This is why it is also a feature of acute nephritis and lupus nephritis, and in fact nephrosclerosis can be produced either by platelet embolization³ or again as a result of intravascular coagulation.⁴ The placenta or trophoblast cells seem to be the only likely source of the thromboplastin that triggers the coagulation process, and I cannot explain post-partum eclampsia other than as a result of the retention of fragments of decidua.^{5,6} A pro-coagulant substance has been isolated from human post-partum serum⁷ and renal lesions of toxæmia can be produced in the rat by the injection of placental extract.⁸ In the paper that we quoted infarcts were found in 67% placentae in toxæmia.⁹

However, I agree with Mr. Sophian that this theory does not explain the hypertension, for which other factors must be invoked and among them the utero-renal reflex. There is accumulating evidence for an association between intravascular coagulation in the kidney and the genesis of renal hypertension. It is true that profound defibrination results in shock and hypotension because of the obstruction of the microcirculation and the vasodilator action of thrombin, but this does not apply to subacute intravascular coagulation.

I anticipate that in the near future somebody will report on the prevalence of microangiopathic red cell fragmentation in pre-eclampsia and eclampsia,¹⁰ on the levels of fibrin products in the circulation, and perhaps also on actual fibrinogen catabolic rates.—I am, etc.,

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Porton Jet Injector

SIR,—In the hope of making full use of our Porton jet injector, I have investigated applications suggested by the suppliers which, besides influenza, propose other mass inocu-

lations, including tetanus toxoid. The injector is supplied with two nozzles—one for intradermal and the other for subcutaneous and intramuscular injections. So far as I could determine from the literature there was no certainty as to the maximum depth of penetration, and before considering the use of this machine for giving intramuscular injections the following study was undertaken.

With the co-operation of Dr. Philip Sheldon, consultant radiologist, Oxford United Hospitals, and with the help of the manufacturer's chief engineer, I received 1 ml. 45% Hypaque (sodium diatrizoate) into the deltoid area. A series of x-ray pictures were then taken to determine the spread and depth of the injection. A block of wood was used to compress the soft tissues in order to demonstrate clearly the thickness of skin, subcutaneous fat, and muscle.¹ As will be seen from the illustration, after the material has penetrated the skin, there is an immediate spread in all directions, and the best that can be expected is for the material to reach the subcutaneous layer.

Perhaps it would reach the muscle in a really thin subject, or a child, but, unless one could predetermine depth penetration for each subject, it might be better to accept the machine as a means of reaching no deeper than subcutaneous regions.—I am, etc.,

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Cowley,
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REFERENCE

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Premedication for Hypotensive Anaesthesia

SIR,—Dr. P. J. Thompson (2 August, p. 300) raises some interesting points regarding hypotensive anaesthesia for micro-aural

surgery. Over the past five years I have anaesthetized some 280 patients for these operations, using hypotensive methods, and I would like to make the following observations.

Adequate microscope haemostasis cannot be achieved unless the systolic blood pressure is dropped to 40 mm. Hg or below. This cannot be done in normotensive patients without the use of a ganglion-blocking agent, and I use pentolinium tartrate (Ansolsen) for this purpose. The average dose administered is 10 mg. in addition to the thiopentone, N₂O and O₂, halothane anaesthetic technique, using a Ruben's valve.

More resistance to hypotension was noticed when atropine premedication was used, and after experimenting over the years I have found Omnopon 10 mg. and Scopolamine 0.4 mg. (hyoscine hydrobromide) one hour preoperatively to be the most satisfactory.

It is difficult to produce adequate hypotension in teenagers, and I have long since given up using hypotensive drugs on patients under 21 years of age.

Instant reversal of hypotension can be achieved by the administration of methylamphetamine 10 mg. intravenously plus 10 mg. intramuscularly. Since the ear is packed after operation no persistent postoperative bleeding has resulted.

Despite the low blood pressure produced no patient has as yet given any anxiety during or after operation. All patients are vetted carefully, and if the slightest suspicion of cardiovascular disease is present no hypotensive technique is used. Likewise not a single patient has shown any cardiovascular complication after operation, in spite of the fact that profound hypotension has been produced for up to one hour's duration. This may be accounted for by the fact that blood loss is virtually non-existent under these conditions.—I am, etc.,

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Cancer Research

SIR,—It is indeed surprising that your recent leading article (5 July, p. 4) summarized the main branches of cancer research in four words—namely, diagnosis, treatment, causation, and prevention. I venture to suggest that the order be reversed, as not enough emphasis is given to prevention where “causes” are known.

The family doctor cannot see what benefits accrue to his patients suffering from cancer, and he has good reason for so thinking. Our patients with cancer do not appear to be living longer. Can anyone show breast cancer survival rates have increased? Has the outlook improved for lung cancer and large bowel and rectal cancer? New operative procedures are not the product of medical research. The fall in death rate from gastric cancer is not shown to be the results of the efforts of workers in the laboratory.

As a general practitioner I wonder what has happened to the suggestions made by Professor P. Beaconsfield (15 October, 1966, p. 948) concerning the shortcomings of the present organization of research, when he wrote that “millions are wasted on cancer research.” This was over two years ago, and in my opinion the millions are still being wasted.

If £26m. are being allocated annually for medical research purposes in the United

Kingdom (and a large proportion of this goes to cancer research laboratories), from the results thus far obtained it is evident that this branch of research needs an agonizing reappraisal. The only people who can do this are the clinicians, because their contact with the patient gives them a sense of drive and urgency which is quite unknown to the scientist in his ivory tower.—I am, etc.,

M. MACLEOD.

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Asymptomatic Bacteriuria in Pregnancy

SIR,—We were interested in the paper by Dr. G. L. Williams and others (26 July, p. 212). One of their main findings was that a defective urinary concentrating ability occurred in 31 (31%) of 100 pregnant women with bacteriuria, but not in non-bacteriuric pregnant control patients. They point out that previous workers have found the incidence of defective concentrating ability to be higher and claim their observations to be new.

However, results almost identical to those of Dr. Williams and his colleagues were reported by us in 1968.¹ Our results showed a defective urine concentrating ability in 30% of 63 patients with bacteriuria in pregnancy but in only 1 of 33 non-bacteriuric pregnant women. The findings of Dr. Williams and colleagues therefore confirm those already reported by ourselves. Incidentally, they also found that the lower limit of concentrating ability in pregnant women without bacteriuria was 750 mOsm/kg. Reference to our paper shows that we had come to the same conclusion.—We are, etc.,

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REFERENCE

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Prolonged Labour

SIR,—The recent article by Dr. Kieran O'Driscoll and others (24 May, p. 477) advocating active management in the first stage of labour emphasizes the changing view towards prolonged labour associated with incoordinate uterine action and posterior positions of the occiput.

On a recent visit to Czechoslovakia sponsored by the Royal College of Obstetricians and Gynaecologists I observed the practice at the Institute for the Care of the Mother and Child in Prague. In 1968, out of 1,002 deliveries only 54 patients laboured longer than 16 hours in the first stage, and only six laboured longer than 30 hours. The incidence of intrapartum foetal death was 1:1,000, the forceps rate was 3%, the caesarean section rate was 4%, and the mean birth weight was 3,350 g.

These results were obtained by a policy of early amniotomy, and oxytocic infusion when progressive cervical dilation ceased. It is interesting that analgesia was used sparingly and consisted mainly of nitrous oxide and pethidine. A senior obstetrician with