Contraceptives and Cervical Carcinoma

SIR,—I have been waiting for comment by someone of authority as a statistician on the paper by Dr. Myron R. Melamed and others (26 July, p. 195) on prevalence rates of cervical carcinoma in situ for women using the diaphragm or contraceptive oral steroids; and I am somewhat surprised that none has so far appeared. Not without some misgivings, therefore, I feel obliged to comment myself on one aspect of the study reported, an aspect I believe to be of fundamental importance.

If I understood the authors' Table I aright, the raw prevalence rates of carcinoma in situ per 1,000 women were 3.8 for those choosing the diaphragm and 6.6 for those choosing oral steroids, *before starting either method of birth control* (column 0; known minimal period of contraceptive use). In other words,

SIR,—I was most interested to read the suggestions put forward by your correspondent, Dr. B. Sandler (9 August, p. 356). It is, of course, well established¹ that cervical cancer is relatively rare among Jewish women. That this low incidence is due entirely to the fact that their husbands are circumcised is not unchallenged. Indeed, the factors that have been proposed as rendering the Jewish woman "different" from the Gentile and thereby less disposed to cervical cancer have been bewildering in their multiplicity and diversity, ranging from the practice of *Niddah* and *Taharâ* (menstrual and post-menstrual abstinence from sexual intercourse)² to the eating of kosher food.³ As far as circumcision is concerned, although in mice it has been shown⁴ that smegma can cause malignant changes, in the human it has been found⁵ that Gentile women who admitted to sexual intercourse with circumcised partners had the same incidence of cervical cancer as the rest of the Gentile population.

It is a subject fraught with intriguing postulations and theories, none of which, as yet, seems to have proved conclusive.—I am, etc.,

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Malignant Granuloma

SIR,—It is a pity that the opportunity was missed in your leading article on malignant granuloma (2 August, p. 254) to develop the point you briefly touched on concerning the use of cytotoxic drugs in this condition. Evidence has been slowly mounting that this may be the treatment of choice, and your remark that "treatment is . . . unsatisfactory" is, I think, unduly gloomy.

In Walton's review¹ of 56 patients, most of whom would not have had steroid treat-

ment, the mean survival was five months. With the benefit of corticosteroids without cytotoxics (but with better antibiotic and chemotherapeutic treatment) the outlook improved somewhat, being just over 12 months in Hollander and Manning's review.² Interestingly, one of the longest survivors that they quoted had in fact been treated with nitrogen mustard in addition (Case 1 in the Table), though another treated with the same combination died at three months. Of their 24 patients treated with corticosteroids alone eight were alive at one year and three were alive after two years.

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G. I. M. SWYER.

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Reported Survival of Patients Suffering from Malignant Granuloma (Wegener's and Lethal Midline) and Treated with Cytotoxic Agents: in Chronological Order

Patient	Reference	Therapy (in Addition to Corticosteroids)	Survival on Therapy in Months	Condition at Time of Reporting
1	3	Nitrogen mustard	40+	Fair
2	4	Cyclophosphamide	24+	Regression of lesions
3	5	Chlorambucil	22+	Normal health
4	5	"	12+	"
5	6	Azathioprine	12+	Normal life at home
6	2	Nitrogen mustard and chlorambucil	12+	Well, at work
7	7	Azathioprine	17+	Asymptomatic
8	7	"	12+	Major improvement
9	8	Azathioprine and Duszomycin	19+	Well, at work
10	8	"	12+	"
11	9	6 M.P.	36	Died following cholecystectomy
12	9	Azathioprine	11+	Regression of lesions
13	10	Azathioprine	24+	Persistent haemoptysis. Successful pregnancy

(+ Indicates that the patient was alive at the time of the report.)

Compare, however, the reported survival of the patients treated with antimetabolic therapy. Although the list is not complete it shows at a glance that the prognosis has been radically changed. All patients were alive at one year and most of them apparently well, and four patients were alive at two years, the drop-out in no case being due to death. Two

patients seen at Brompton Hospital also appear to have benefited. One, a young man in extremis in spite of 80 mg. of prednisone a day for three months, entered a good remission with healing of lesions on azathioprine 3 mg./kg./day. An intercurrent infection led to the azathioprine being stopped; there was a relapse, and at necropsy it was found that there were two generations of lesions, the one old and fibrotic and the other recent and active. I think that now the prednisone rather than the azathioprine would be reduced in such circumstances. The second patient (Case 13 in the Table) is maintained in remission by 2 mg./kg. of azathioprine per day, and has recently, under the care of Mr. Kenneth Cooper at Southlands Hospital, Shoreham, given birth to a normal child. Her only complaint at present is persistent haemoptysis.

Until someone produces survival figures for patients treated with corticosteroids alone as good as those in the Table, I don't think there can be any justification for withholding antimetabolic therapy from patients with this condition.—I am, etc.,

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Progestogen-only Oral Contraceptives

SIR,—I would like to make certain comments in relation to the recent paper by Dr. Eleanor Mears and others (21 June, p. 730) on the use of mini-dose progestogens in fertility control, particularly as I was partly responsible for the selection of dosage of megestrol acetate used in this study in Yugoslavia. Studies with megestrol acetate at a dosage of 0.5 mg. daily had proved reasonably effective in the United Kingdom,¹ Australia,² and elsewhere. Preliminary clinical studies with 0.25 mg. daily were encouraging, and, following preliminary studies by Swyer³ at this dosage, cervical mucus consistency was increased and postcoital tests showed an absence or marked reduction in sperm activity in most instances. From these accumulated data it was clearly desirable to obtain more extensive clinical data in a country where legalized abortion was generally available.

The Yugoslav study demonstrated most lucidly that megestrol acetate at a dosage of 0.25 mg. daily is quite ineffective, 21 of the 43 women in the study becoming pregnant in 223 cycles studied—a pregnancy rate of 12.6. In the same study postcoital examinations gave results similar for all the compounds used, the other three being much

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 thrombosis 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 toxemia 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 toxemia.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-