E. Sheehan, R. Shanahan, and P. Scully. In Cork: Drs. B. Foley, J. Magner, C. Wright, and Mr. P. Flaherty. In Waterford: Drs. K. Hickey, T. Keogh, and J. Walsh. In Limerick: Dr. J. Nash. In London: Professor G. S. Nelson. We wish to thank Professor Z. Kozar, Wrocław, Poland, for bibliographic summaries.

REFERENCES

- Adamczyk, J., and Osuch, T. (1961). *Przegląd Epidemiologiczny*, **15**, 399.
- Aikawa, J. K. (1966). In *Current Diagnosis*, edited by H. F. Conn, R. J. Clohocy, and R. B. Conn, p. 101. Philadelphia and London, Saunders.
- Beck, J. W., and Beverley-Burton, M. (1968). *Helminthological Abstracts*, **37**, 1.
- Britov, V. A. (1962). *Zoologicheskii Zhurnal*, **41**, 776.
- Brown, H. W. (1967). In *Cecil-Loeb Textbook of Medicine*, edited by P. B. Beeson, and W. McDermott, 12th ed. Philadelphia and London, Saunders.
- Campbell, W. C. (1961). *Journal of Parasitology*, **47**, No. 4, Section 2, p. 37.
- Campbell, W. C., and Cuckler, A. C. (1962). *Journal of Parasitology*, **48**, No. 2, p. 28.
- Campbell, W. C., and Cuckler, A. C. (1964). *Journal of Parasitology*, **50**, 481.
- Corridan, J. P., and O'Meara, P. B. (1968). *Irish Journal of Medical Science*, 7th series, **1**, 109.
- Day, C. L., Wood, E. A., and Lane, W. F. (1946). *Journal of the Royal Army Medical Corps*, **86**, 58.
- Drury, M. I. (1957). *Irish Journal of Medical Science*, 6th series, **7**, 84.
- Forrester, A. T. T., Nelson, G. S., and Sander, G. (1961). *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **55**, 503.
- Furnell, M. J. G. (1957). In *Annual Report of the Medical Research Council of Ireland*.
- Gancarz, Z. (1961). *Przegląd Epidemiologiczny*, **15**, 1.
- Glontz, G. E., and Saslaw, S. (1968). *Archives of Internal Medicine*, **122**, 445.
- Gould, S. E. (1945). *Trichinosis*. Springfield, Illinois, Thomas.
- Hall, M. C. (1937). *Public Health Reports*, **52**, 539.
- Imnella, F., and Redner, W. J. (1959). *Journal of the American Medical Association*, **171**, 885.
- Kean, B. H. (1967). *Annals of Internal Medicine*, **67**, 461.
- Lamina, J., and Schoop, G. (1966). *Berliner und Münchener tierärztliche Wochenschrift*, **79**, 34.
- Leinati, L., and Marazza, V. (1959). *Clinica Veterinaria (Milano)*, **82**, 1.
- McGill, D. A. (1957). *Guy's Hospital Reports*, **106**, 92.
- Most, H. (1965). *Journal of the American Medical Association*, **193**, 871.
- Nash, J., Kidney, J. G., Furnell, M. J. G., and O'Meara, P. B. (1957). *Journal of the Irish Medical Association*, **40**, 74.
- Nelson, G. S. (1968). In *Some Diseases of Animals Communicable to Man in Britain*, edited by O. Graham-Jones, p. 77. Oxford, Pergamon Press.
- Nelson, G. S., Guggisberg, C. W. A., and Mukundi, J. (1963). *Annals of Tropical Medicine and Parasitology*, **57**, 332.
- Norman, L., and Kagan, I. G. (1963). *Public Health Reports*, **78**, 227.
- Oldham, J. N., and Beresford-Jones, W. P. (1957). *British Veterinary Journal*, **113**, 34.
- Ozeretskovskaya, N. N. (1965). *Meditinskaya Parazitologiya i Parazitarnye Bolezni*, **34**, 379.
- Pigs and Bacon Commission, Ireland (1967). Annual Report.
- Rausch, R., Babero, B. B., Rausch, R. V., and Schiller, E. L. (1956). *Journal of Parasitology*, **42**, 259.
- Redahan, E. (1967). *Irish Veterinary Journal*, **21**, 168.
- Robinson, H. A., and Olsen, O. W. (1960). *Journal of Parasitology*, **46**, 589.
- Roselle, H. A., Schwartz, D. T., and Geer, F. G. (1965). *New England Journal of Medicine*, **272**, 304.
- Schnurrenberger, P. R., Masterson, R. A., Suessenguth, H., and Bashe, W. J. jun. (1964). *American Journal of Veterinary Research*, **25**, 174.
- Schwabe, C. W. (1964). *Veterinary Medicine and Human Health*. Baltimore, Williams and Wilkins.
- Semple, A. B., Davies, J. B. M., Kershaw, W. E., and St. Hill, C. A. (1954). *British Medical Journal*, **1**, 1002.
- Silverman, P. H., and Griffiths, R. B. (1955). *Annals of Tropical Medicine and Parasitology*, **49**, 436.
- Spink, W. W., and Augustine, D. L. (1935). *New England Journal of Medicine*, **213**, 527.
- Stone, O. J., Stone, C. T., and Mullins, J. F. (1964). *Journal of the American Medical Association*, **187**, 536.
- Van Someren, V. D. (1937). *British Medical Journal*, **2**, 1162.
- Zaiman, H., Ingalls, J. W., jun., and Villaverde, H. (1962). *Experimental Parasitology*, **12**, 418.
- Zimmerman, W. J., Hubbard, E. D., Schwarte, L. H., and Biester, H. E. (1962). *Cornell Veterinarian*, **52**, 156.

Preliminary Evaluation of Four Oral Contraceptives Containing only Progestogens

ELEANOR MEARS,* M.B., CH.B.; M. P. VESSEY,† M.B., B.S.; LIDIJA ANDOLŠEK,‡ M.D.; ANTONIJA OVEN‡

British Medical Journal, 1969, **2**, 730-734

Summary: One hundred and seventy-five women took part in a comparative clinical trial of four progestogen-only oral contraceptives and were followed for either a year or until treatment was discontinued. Megestrol acetate 0.25 mg. was found to be a very ineffective contraceptive, 21 out of 43 women becoming pregnant. One, three, and four pregnancies occurred during treatment with norethisterone acetate 0.3 mg., norgestrel 0.05 mg., and chlormadinone 0.5 mg., respectively, corresponding to pregnancy rates of 4, 9, and 12 per 100 woman-years of use.

All three effective progestogens were very much less acceptable than modern low-dose combined oral contraceptives. Discontinuation of treatment for medical reasons (particularly menstrual disturbances) during the course of only one year affected 24% receiving norethisterone acetate, 38% receiving norgestrel, and 46% receiving chlormadinone.

* 111 Harley Street, London W.1.

† Member, Scientific Staff, Medical Research Council's Statistical Research Unit, London W.C.1.

‡ Family Planning Institute, Ljubljana, Yugoslavia.

Introduction

A small dose of an orally active progestogen administered every day throughout the menstrual cycle exerts a pronounced antifertility effect which so far has not been adequately explained. Ovulation is certainly not regularly inhibited by such medication, and changes in the endometrial morphology seem to be minor and variable. Alterations in the physico-chemical properties of the cervical mucus occur fairly consistently, but are thought to be insufficient to account entirely for the contraceptive action.

Previous laboratory and clinical experience with the available orally active progestogens has shown that each has a different dose-related range of hormonal activity with varying effects on the ovaries, Fallopian tubes, uterus, cervix, and vagina. The problem is to find a dose of some progestogen, if such exists, which will prevent conception without interfering with the menstrual cycle and with the endogenous hormonal pattern. Rudel *et al.* (1965) considered the most promising substances to be the 17 α -hydroxyprogestogens, which do not inhibit ovulation in the doses at present used for contraception. These substances have strong progestational

and antioestrogenic activity and might be expected to have a maximum effect on the endometrium and cervical secretions.

While detailed biochemical and other laboratory exploration should continue, comparative clinical trials of several progestogens known to have different effects on the various end-organs may clarify their mode of action and indicate their clinical value as contraceptives. Yugoslavia is a country well suited to such research, because the women there are relatively new to family planning and have not had much previous experience of conventional methods. Further, abortions, though still available legally, are now being discouraged in favour of prevention of pregnancy by family planning.

Ljubljana was chosen as a suitable centre to start the present work because there is a well-established Family Planning Institute there with trained medical and ancillary staff and a statistician.

Material and Methods

The products chosen for the present trial were norethisterone acetate 0.3 mg., norgestrel 0.05 mg., chlormadinone 0.5 mg., and megestrol acetate 0.25 mg.

Since the manufacturers could not make supplies of all these substances available at the same time and because the present trial was regarded principally as a pilot investigation, women were recruited to the four treatment groups over different periods of time rather than at random. Furthermore, apart from using code letters instead of the names of the individual progestogens, no attempt was made to make the trial "blind," either to the doctors or to the patients. It may be noted, however, that all the tablets used were of similar size, shape, and colour.

The requirements for women enrolled in the trial were: aged 18 to 40; of proved fertility, with no more spontaneous abortions than liveborn children; having taken no hormones or oral contraceptives during the previous two months; normal on gynaecological examination; free from chronic liver disease, allergic disorders, or epilepsy; and having no history of thromboembolic disease.

At the first visit a full medical, obstetrical, and gynaecological history was obtained by using a standard questionnaire. Each patient was also given a routine physical examination to exclude overt disease. She was then provided with a bottle containing 60 tablets of one of the products and told to start taking them on the first day of her next menstrual period, to continue to take one tablet daily, and to return to the clinic a few days before her supply ran out. She was also given a personal record card on which to keep a daily record of tablets taken, bleeding, etc. She was told to take the tablets at the time of day when she would be most likely to remember them, but, if she forgot one, to take it as soon as she did remember.

The first follow-up visit was usually made at about six weeks, then two months later, then every three months. The aim in this pilot trial was to follow each subject for one year. At each visit details from the personal record card were checked with the patient and progress was recorded on a follow-up form. Those who failed to keep their appointments were contacted by telephone or letter and if this failed to produce a response they were visited at home. All observations were made in the same way by the same interviewers, standard questionnaires being used throughout the period of the study. Some patients on each product were also subjected to postcoital tests and endometrial biopsies.

It was decided to eliminate the term "breakthrough bleeding" from the recording because it did not seem appropriate with the medication used, as the normal cyclic bleeding pattern

is altered. Any bleeding which was sufficient to require the use of a sanitary pad or tampon was recorded as menstrual bleeding, and the first day of such bleeding was regarded as the first day of a menstrual cycle. Any bleeding which was less than this and which required no sanitary protection was regarded as "spotting."

A total of 175 women were admitted to the trial, the numbers in each treatment group being about equal (Table I). Every woman was successfully followed until either one year of medication had been completed or treatment was discontinued for some reason. Although this was not a randomized trial, analysis of the data concerning age, number of pregnancies, cycle length, duration of menstrual flow, menstrual discomfort, and intermenstrual bleeding, which were recorded for each woman at the first interview, did not show any statistically significant pretreatment differences between the groups. Direct comparison of the effects of the four progestogens therefore seems justified, but there may have been bias in this trial that we have been unable to detect.

TABLE I.—Number of Women Discontinuing Contraceptive Treatment for Various Reasons

	Treatment Group			
	Nor-ethisterone	Norgestrel	Chlor-madinone	Megestrol
No. of women starting treatment	41	45	46	43
No. of women discontinuing treatment on account of:				
Pregnancy	1	3	4	21
Menstrual disturbance	4	9	13	0
Other side-effects	5	5	4	1
Reasons unconnected with treatment	12	5	7	7
Withdrawal by clinic	0	0	0	14*
No. of women completing one year's treatment	19	23	18	0

* All after at least 6 completed months of treatment.

Results

Clinical Findings

Table I shows the number of women completing one year's medication and also indicates the principal reasons why the other women withdrew from the trial. No fewer than 21 of the 43 patients treated with megestrol acetate (0.25 mg.) became pregnant, and only three of these pregnancies are known to have followed the omission of tablets. Two women taking megestrol acetate became pregnant during the first cycle of medication, while six of the remaining pregnancies occurred after four or more cycles of treatment had been completed.

One, three, and four pregnancies occurred during treatment with norethisterone acetate, norgestrel, and chlormadinone respectively, corresponding to pregnancy rates of 4, 9, and 12 per 100 woman-years of use. None of these women became pregnant during the first treated cycle but three did so after completing at least four cycles of medication. Only two pregnancies (one each in the norgestrel and chlormadinone groups) are known to have followed omission of tablets.

Reasons for withdrawal from the trial other than for pregnancy are rather overshadowed among the women treated with megestrol acetate, though it may be noted that only one of them discontinued treatment because of side-effects of any sort. In the other three groups menstrual disturbances commonly led to withdrawal from the trial, especially among women treated with chlormadinone, and other side-effects caused about 10% of women in each group to stop treatment.

The general pattern of variation in menstrual cycle length is shown for each treatment group in Table II. It should be

noted that these data, which are based on the total number of cycles observed, are biased to an unknown extent by the selective discontinuation of treatment by some women (Table I). Nevertheless, it is apparent that none of the four progestogens investigated provided nearly such satisfactory cycle control as combined oral contraceptives. The latter, however, are known to correct the irregular cycles often experienced by normal women, and Foss *et al.* (1968) suggested that a more appropriate comparison may be provided by the menstrual pattern in untreated women. Data collected by Chiazzie *et al.* (1968), which agree fairly well with those given by other workers (see Treloar *et al.*, 1967), have therefore also been shown in Table II. On this basis a major fault of contraceptives containing a progestogen alone is seen to be their tendency to produce an excess of short cycles. This effect was particularly prominent in the group of women treated with norgestrel, while those given megestrol acetate experienced cycles that were not very different in duration from those in untreated women.

TABLE II.—Percentage Frequency Distribution of All Cycles Observed in Each Treatment Group by Cycle Length

Length of Cycle (Days)	Treatment Group				Untreated Women*
	Norethisterone	Norgestrel	Chlormadinone	Megestrol	
Up to 17	6.4	12.5	10.6	2.7	1.1
18-24	14.7	23.3	13.1	12.1	9.9
25-31	60.1	49.9	59.8	64.6	69.1
32-38	12.1	11.3	12.6	14.3	13.9
39 or more	6.7	3.0	3.9	6.3	6.0
No. of cycles ..	328	433	406	223	30,655
Mean cycle length ..	28.3	25.9	27.1	28.8	29.4

* Calculated from data given by Chiazzie *et al.* (1968) to correspond with the overall age distribution of women included in the present trial.

Of more importance than the overall pattern of cycle length is the way in which individual women fared. Examination of the distributions of median cycle length for individual women confirmed the impression given by Table II that those treated with norgestrel had a special tendency to experience short cycles. A rough measure of menstrual regularity was obtained by calculating the range of variation in cycle length for every woman completing four or more cycles of treatment. The results, shown in Table III, indicate the extremely variable cycle length experienced by most women taking any of the four progestogens, though megestrol acetate was notably better than any of the other three in this respect, even when the shorter period of follow-up experienced by the women given that treatment is taken into account. To find out whether the irregular menstrual pattern was due to the influence of the odd cycle of discrepant length, the ranges were recalculated, the furthest outlying value being omitted in every case. These results, which still show wide variation, are also shown in Table III, but in parentheses.

TABLE III.—Variation in Range of Cycle Length for Individual Women Completing at Least Four Cycles of Treatment. Data Shown are Percentages of Women in Each Treatment Group

Difference Between Lengths of Longest and Shortest Cycles (in Days)	Treatment Group			
	Norethisterone	Norgestrel	Chlormadinone	Megestrol
Up to 7	21 (43)	26 (39)	14 (42)	38 (73)
8-14	18 (29)	18 (32)	22 (31)	31 (15)
15 or more	61 (28)	56 (29)	64 (27)	31 (12)
No. of women ..	28	38	36	26

Numbers in parentheses are results obtained when ranges are recalculated, omitting in every case the furthest outlying value.

Further analyses, which are not given here, did not show any tendency for cycle length or regularity to alter with increasing duration of treatment in any of the four groups.

The duration and amount of menstrual flow were usually acceptable to the women in each treatment group. Once again, however, those treated with megestrol acetate had the most favourable experience, with only 2% of menstrual periods lasting seven days or more. Corresponding percentages in the other groups ranged from 5 (in the norgestrel group) to 15 (in the chlormadinone group).

Intermenstrual spotting occurred during the first cycle of treatment in about one-quarter of the women receiving norethisterone acetate, norgestrel, or chlormadinone, but in only 5% of those given megestrol acetate. The incidence of spotting was reduced by about one-half in cycles subsequent to the first in all treatment groups, though, particularly among those treated with chlormadinone, it continued to be high enough to be troublesome.

Although 15 women dropped out of the trial because of side-effects other than those associated with menstruation (Table I), the recorded incidence of most of the minor disturbances commonly caused by oral contraceptives was fairly low (Table IV). About 60% of the patients treated with norethisterone acetate, norgestrel, or chlormadinone were entirely free from such side-effects throughout the trial. The commonest complaints in these three groups were nausea or vomiting, breast tenderness, and headache; the incidence of these side-effects was remarkably consistent from group to group. Side-effects were noted only about half as frequently by the women given megestrol acetate, an observation only partially explained by the shorter average period of follow-up for the subjects in this group.

TABLE IV.—Percentages of Women in Each Group Suffering from Certain Side-effects at Any Time During the Course of Treatment

Side-effect	Treatment Group			
	Norethisterone	Norgestrel	Chlormadinone	Megestrol
None	56	58	61	77
Nausea or vomiting	12	13	9	5
Breast tenderness	17	16	15	7
Headache	10	9	11	5
Any other	24	22	22	12

None of the four progestogens had any consistent effect on body weight and no serious adverse reactions were observed.

Endometrial Biopsies

Altogether 89 biopsy specimens were obtained during the study, each of which was subsequently examined by two experienced observers. The effect of the constant small progestogenic stimulus on the endometrium throughout the cycle was varied, but usually of one of two kinds. In some instances the endometrium was normal for the stage of the cycle at which the biopsy specimen was taken. In others the appearance was similar to that produced by an intermediate type of combined oral contraceptive (Grant, 1964, 1967), showing a predominantly progestogenic effect with the proliferative and early secretory stages prolonged and occurring simultaneously without either maximal growth or involution.

There were, however, some differences between the products investigated, and these may be summarized as follows:

Norethisterone Acetate (19 Biopsies).—Four biopsies were normal for the stage in the cycle, and the one patient who became pregnant had previously had a normal early secretory endometrium on day 15. Two specimens taken from other patients on days 42 and 52 had proliferative changes suggesting delayed ovulation. This was the most strongly progestogenic of the four products as shown by the relatively short growth phase and the early appearance of subnuclear vacuoles followed by a prolonged postsecretory phase and pronounced atrophy, the latter found as early as day 14 in some cases.

Norgestrel (28 Biopsies).—There were a few normal specimens suggesting mid-cycle or delayed ovulation, but the overall effect was similar to that of a weak progestogen with oestrogen—that is, a progestogenic effect was observed in the endometrium during the proliferative phase and there were continuing proliferative changes along with the small subnuclear vacuoles in the early secretory stage. The early and mid-secretory phases were more extended than with the other products. Norgestrel also had the most pronounced effect on the blood vessels in the endometrium, with a high density of well-developed arterioles, dilated sinusoids, and condensation around the sinusoids.

Chlormadinone (26 Biopsies).—The general effect of this product was again similar to that of a weak progestogen with oestrogen. Some normal ovulatory cycles were found but no evidence of delayed ovulation. The postsecretory phase was prolonged, but there was no evidence of atrophy and all specimens contained at least some fragments with columnar glands.

Megestrol Acetate (16 Biopsies).—All except three of these specimens had more plentiful tissue than those taken from the patients on the other three products. The majority were compatible with a more or less normal endometrium with mid-cycle ovulation. Unfortunately there were no specimens later than day 19, so that the effect on the latter part of the cycle was not observed save for one biopsy taken on day 41, which showed trophoblastic tissue.

Postcoital Tests

Table V summarizes the results of tests made at mid-cycle. Each test was assessed by the Margaret Sanger classification (Sujan *et al.*, 1963). All the products had an antifertility effect on the cervical mucus, though norgestrel, chlormadinone, and megestrol acetate each gave a few results compatible with normal fertility. Norethisterone acetate appeared to have the most pronounced effect on the cervical mucus. It should also be noted that though 21 pregnancies occurred among women taking megestrol acetate, the postcoital test results with this product were very similar to those with norgestrel and chlormadinone, which were much more effective contraceptives.

TABLE V.—Results of Mid-cycle Postcoital Tests (Margaret Sanger Classification)

Treatment Group	No. of Tests	No. of Tests Classified				
		Negative	Poor	Fair	Good	Excellent
Norethisterone	10	4	6	0	0	0
Norgestrel ..	22	9	9	2	2	0
Chlormadinone	13	4	5	0	3	1
Megestrol ..	16	5	8	2	1	0

Outcome of Pregnancies

The total number of women becoming pregnant was 29, of whom eight decided to continue with the pregnancy. The remaining pregnancies were terminated surgically. All the eight infants have been delivered; seven are normal and one has a minor malformation of one foot. The products of conception obtained during the first six terminations were examined histologically: all were found to be normal. No macroscopic abnormality was noted in the remainder.

Discussion

One incontrovertible finding in the present trial is that megestrol acetate in the dose used (0.25 mg.) is a very ineffective contraceptive, and in further work now in progress we have increased the dose to 0.7 mg.

The "use-effectiveness pregnancy rate" (in the calculation of which all unintentional pregnancies are included) was also appreciable with the other three progestogens. For chlor-

madinone the rate was 12 per 100 woman-years, a figure higher than that reported by Martinez-Manautou *et al.* (1967a, 1967b), Connell (1967), and Zañartu *et al.* (1968), all of whom recorded rates in the range of 1–7 per 100 woman-years. It should be noted, however, that overall pregnancy rates calculated in terms of "woman-years" are very much influenced by duration of follow-up, since most pregnancies occur during the early months of contraception. Furthermore, our rate is based on small numbers and is statistically quite compatible with the results recorded by others. We are unaware of any published rates for norethisterone acetate, but for norgestrel our figure of 9 per 100 woman-years (based on three pregnancies) is higher than that of 3 per 100 woman-years (based on six pregnancies) found by Foss *et al.* (1968).

Not surprisingly, megestrol acetate in the dose used produced much less disturbance in the menstrual pattern and in the endometrium and fewer side-effects of any sort than any of the other three progestogens. It is of some interest, however, that the results of the postcoital tests for patients taking the ineffective dose of megestrol acetate were very similar to those relating to the other three preparations. This result, admittedly based on very small numbers, does raise the question that perhaps the cervical factor is not as important for contraceptive efficiency as is sometimes claimed.

Chlormadinone was associated with the highest discontinuation rate for menstrual disturbances and also gave the most trouble with prolongation of the menstrual flow and intermenstrual spotting. Norgestrel had a particular tendency to produce very short cycles, an observation also made by Foss *et al.* (1968), and had the most pronounced vascular effect on the endometrium. The high incidence of short cycles with norgestrel is consistent with the endometrial finding of a long secretory phase with subnuclear vacuoles, extending into the later parts of the cycle, which Grant (1967) found to be associated with a high incidence of breakthrough bleeding with the combined oral contraceptives. On balance, norethisterone acetate gave the most promising results in this preliminary assessment and had the most pronounced effect both on the cervical secretions and on the endometrium.

Of more importance than these detailed differences between the three effective progestogens, all of which await confirmation in the larger double-blind trial which we have now started, is the fact that all three were much less satisfactory than the modern low-dose combined oral contraceptives. Medical reasons for discontinuation (including pregnancy) during the course of only one year affected from 24% (norethisterone acetate) to 46% (chlormadinone) of women.

There are, of course, many difficulties in comparing the acceptance of a method of contraception between groups of women living in countries differing in social, cultural, and religious background, but it may be noted that our results are less satisfactory than those quoted by the other workers to whom we have already referred. Among the factors which may have contributed to this difference is the availability of legal abortion in Yugoslavia, which may have caused the women in our investigation to have been less motivated towards contraception than those in some other countries.

In conclusion, it is our present view that the continuous progestogen regimens available, though satisfactory for some women, are unlikely to offer a serious challenge to the existing methods of oral contraception, despite the advantages of simplicity, low cost, and, possibly, a reduced risk of serious adverse reactions. Contrary to the earlier hopes of Rudel *et al.* (1965), it may well be that for a dose of progestogen to be effective as a contraceptive some interference with menstrual regularity and other side-effects have to occur as a result of hormonal changes and sometimes even of inhibition of ovulation.

We should like to thank Dr. Srećko Rainer and Dr. Ellen Grant for examining the endometrial biopsy specimens and Dr. Cizelj for assessing the results of the postcoital tests. Miss Rosemary Emerson assisted with the statistical analysis.

We should also like to acknowledge the financial assistance given by the Population Council, British Drug Houses Ltd., Schering Chemicals Ltd., Syntex Pharmaceuticals Ltd., and John Wyeth and Brother Ltd. kindly provided the contraceptive tablets.

REFERENCES

- Chiazze, L., Brayer, F. T., Macisco, J. J., Parker, M. P., and Duffy, B. J. (1968). *Journal of the American Medical Association*, **203**, 377.
- Connell, E. B. (1967). In *Advances in Planned Parenthood*, edited by A. J. Sobrero and S. Lewit, p. 74. New York, Excerpta Medica.
- Foss, G. L., Svendsen, E. K., Fotherby, K., and Richards, D. J. (1968). *British Medical Journal*, **4**, 489.
- Grant, E. C. G. (1964). *Journal of Reproduction and Fertility*, **8**, 275.
- Grant, E. C. G. (1967). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **74**, 908.
- Martinez-Manautou, J., Giner-Velasquez, J., Aznar-Ranios, R., Lozano-Balderas, M., and Rudel, W. H. (1967a). In *Proceedings of the 8th International Conference of the International Planned Parenthood Federation*. London, I.P.P.F.
- Martinez-Manautou, J., *et al.* (1967b). *British Medical Journal*, **2**, 730.
- Rudel, H. W., Martinez-Manautou, J., and Maqueo-Topete, M. (1965). *Fertility and Sterility*, **16**, 158.
- Sujan, S., Danezis, J., and Sobrero, A. J. (1963). *Journal of Reproduction and Fertility*, **6**, 87.
- Treloar, A. E., Boynton, R. E., Behn, B. G., and Brown, B. W. (1967). *International Journal of Fertility*, **12**, 77.
- Zañartu, J., Rodriguez-Moore, G., Pupkin, M., Salas, O., and Guerrero, R. (1968). *British Medical Journal*, **2**, 263.

Reproductive Potential of Patients Treated by Maintenance Haemodialysis

M. ELSTEIN,* M.B., CH.B., M.R.C.O.G.; E. K. M. SMITH,† M.D., B.S.C., M.R.C.P.; J. R. CURTIS,† M.D., M.R.C.P.

British Medical Journal, 1969, **2**, 734-736

Summary: Three of the wives of 25 men undergoing maintenance haemodialysis for terminal renal failure became pregnant. This suggests that fertility is not necessarily impaired in these patients and that contraceptive methods should be used by women patients at risk.

Introduction

It is commonly stated that patients with severe chronic renal failure are either sterile or strikingly subfertile. Amenorrhoea often occurs in women, and in men impotence is a common complaint (Schreiner and Maher, 1965). While the abnormal chemistry of the uraemic state may have some specific effects on ovulation and spermatogenesis, patients with severe renal failure are suffering from a chronic and debilitating disease, whose effects on reproductive processes may be entirely non-specific.

Until recent times such patients seldom survived very long; hence the emotional and social consequences of their infertility were not great. The development of facilities for maintenance haemodialysis, however, has offered such patients an opportunity to return to a more useful life and often to productive work (Curtis *et al.*, 1969). In this situation the question of sexual potency and fertility becomes much more relevant, both to the patient, who regards it as an important part of his return to a more normal life, and to the physician, who has to handle the pregnancies that may arise. It is clearly no longer justifiable to assume that the infertility and impotence of the uraemic state continue when maintenance dialysis is begun, for there have been occasional reports of male patients successfully impregnating their wives. There is, however, no record of a successful pregnancy occurring in a woman treated by long-term dialysis. This paper reports three instances of pregnancy occurring in the spouses of men who have terminal renal failure, and who have been satisfactorily maintained by haemo-

dialysis. In addition, an investigation of the sexual activity of 35 patients on maintenance haemodialysis indicates that a significant number of them are able to enjoy an active sexual life.

The Patients

Since March 1964 41 patients have been treated by maintenance haemodialysis at Fulham Hospital; of these, 35 were available for the present study. Twelve treat themselves in the home, while the remainder are dialysed in hospital; all have at least 28 hours of dialysis each week by means of a Kiil dialyser and a single-pass warm dialysate system (Curtis *et al.*, 1969). Access to the blood stream is by a standard Teflon-Silastic arteriovenous shunt. Among the patients reviewed there were 25 men and 10 women.

In six of the women normal periods returned after the start of dialysis, and in four instances an x-ray menopause has been induced because of the exacerbation of their anaemia due to prolonged and heavy periods. None of our female patients has become pregnant; two have been seen for disturbances of sexual function because they both experienced a diminution of libido after radiotherapy. They were treated with vaginal oestrogen cream (dienoestrol) and given advice on sexual techniques. They are both now achieving satisfactory relations, with orgasm—an improvement on their performance before they became ill.

Pregnancy has, however, occurred in the wives of three male patients; all three have successfully delivered normal babies.

Case 1

This patient was first seen at the age of 22 with acute glomerulonephritis, and over the next two years had five episodes of haematuria; he then remained well until he developed nocturia and thirst at the age of 30 and was found, a year later, to be hypertensive, anaemic, and to have a blood urea of 300 mg./100 ml. He was started on maintenance haemodialysis at this time, and his renal failure has been well controlled, though his first year of treatment was marred by the development of progressive deafness,

* Lecturer in Obstetrics and Gynaecology.

† Senior Lecturer in Medicine.

Charing Cross Hospital Medical School, London W.6.