

FISUM SATIVUM (LINN):

THE EFFECT OF m-XYLOHYDROQUINONE ON "FUNCTIONAL BLEEDING"

(HUMAN TRIAL)

S.N. Sanyal, B.Sc., M.B.

ORIGINAL COMMUNICATIONS

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Introduction

No previously known chemical agent is able to antagonise directly the female sex hormones, estrogen and progesterone. These sex hormones are synergistic up to a certain proportions and beyond that are antagonistic to each other (PARKES *et al*, 1928; FEVOLD *et al*, 1936; LIPSCHUTZ *et al*, 1936). This has given incentive to the search for a contraceptive using female sex hormones either orally or by parenteral route. Excess of estrogen inhibits the liberation of estrogen (HISAW *et al*, 1934) and brings about sterility for a certain period of time. Sheep fed on clovers become sterile. A similar action is seen with excess of progesterone. In clinical practice this principle has been used in certain feminine disorders, but the desired effect is marred to a great extent due to the behaviour of the anterior pituitary. When the secretion of estrogen is beyond a certain optimum, anterior pituitary inhibits its secretion and stimulates the secretion of progesterone through LH (LANE and HISAW, 1934; BURROWS, 1949); and when progesterone is in excess, it liberates FSH to stimulate the secretion of estrogen (SMITH *et al* 1932; CORNER, 1935). Again chorionic gonadotropin or estrogen is useful in climacteric conditions (HELLER *et al*, 1944) but its prolonged administration is attended with the risk of possibility of carcinoma formation (Hamblen, 1947). Excessive estrogen is also a contributing factor in some forms of carcinoma in the female, especially of the breast and female genitals. OBERLING (1944), NICHOLSON, TAYLOR (1930), ALLEN *et al*, AUCHINCLOS *et al* (1940), LACASSAGNE (1936, 1938), GARDNER (1941), CORI (1927), LOEB (1919), HISAW & LENDRUM (1936). In menorrhagia which is due to hormonal imbalance only, male sex hormone (testosterone) is useful (ZUCKERMAN and PARKES, 1936; ROBSON, 1936; ZUCKERMAN, 1937; GARDNER, 1946; PAPANICOLAOU *et al*, 1938) but its continued use is also discouraged in the case of the females.

In my previous communications (SANYAL, 1949, 1950, 1951, 1952, 1953, 1954, 1955), it has been pointed out that m-xylohydroquinone neutralises progesterone, the effect being manifested in the endometrial glands. Recently attempts have been made to find out whether this can also counteract estrogens. This will form the subject matter of the present paper. This was also suggested some time ago by Dr. H. L. MASON of the Mayo Clinic, Rochester, Minnesota, U.S.A. and also by Prof. RALF. I. DORFMAN of the Worcester Foundation for Experimental Biology, Shrewsbury, Mass., U.S.A.

Clinical Conditions

Some clinical conditions are observed in young females, unmarried or married, where the menstrual flow is pro-

longed for many days and is attended with heavy discharge of blood. Prolonged loss of blood tells upon the general health and some active interference becomes urgent. This type of bleeding, menorrhagia and metrorrhagia, is experienced by many women at various stages of their sexual life, at various ages and particularly during menopause. When no other pathological findings are available, such as fibroid growth etc., this is generally known as functional bleeding or endometrial hyperplasia.

According to BOYD (1947) irregular uterine bleeding in women—profuse, periodic or continuous, in young women and in menopause is due to endometrial hyperplasia. According to SCHRODER (1915) and many others this is known as ovarian disfunction due to pathological persistence of ripening follicle. Menstruation is not essentially dependant on ovulation, and in the absence of ovulation there is no biphasic changes of the endometrium and no formation of desidual tissue. Thick endometrium is found in curettage with sometimes papillary excrescences and is markedly glandular in appearance. The arrangement of the glands are disorderly with variations in size and shape, the epithelium being several layers thick. Muscular layers are often invaded by the glands. Gradually cystic degeneration takes place in the deeper layers of the glands and has the appearance of "Swiss cheese". Stroma cells show numerous mitosis and marked vascular congestion and edema with complete absence of decidual reaction. Bleeding is initiated by necrosis which is patchy in the superficial layer and there is thrombosis of small vessels. There may be extensive infiltrations of polymorph cells, but there is complete absence of plasma cells. These changes are all due to hyperestrinism and over-stimulation which leads to thrombosis. The cause of necrosis may also be due to corpus luteum influence. Corpus luteum overactivity may also bring about excessive uterine bleeding. BURCH, WILLIAMS and CUNNINGHAM (1931), WOLFE *et al* (1932), HORNING (1942-44), ASTWOOD (1938, 1939), also observed similar changes in the endometrium after injections of estrin or corpus luteum extracts in animals (1931).

Case Reports

With the idea that m-Xylohydroquinone which can neutralise the effect of progesterone, can also counter-act estrogen, attention was directed to determine its clinical effect in such cases. Very few patients volunteered, the available cases being generally in an aggravated stage, where other methods of treatment had shown discouraging results. But in any case it was very difficult to submit to operational measures even as simple as diagnostic

curetting, because of the absence of any hospital facilities. Still two specimens of endometrial biopsy were secured.

Case Histories

Case No. 1: Patient, A.D., aged 19 years, F.M. 12 years. L.M. was continuous for 17 days and profuse. The patient had practically bled white and complained of giddiness while standing up. Standard methods of treatment were tried for three days with no visible effect. On the nineteenth day of bleeding, one capsule of m-Xylohydroquinone was given at night and the next morning there was practically no bleeding. A second capsule was also administered next day. For the next six months, periods were regular and normal but again there was profuse bleeding in the seventh month. Again one capsule was given on the seventh day of bleeding, which stopped the bleeding the next day. After this, the periods were regular but the condition aggravated again after six months. This time diagnostic curettage was taken by Dr. D. N. BANERJEA of the Chittaranjan Seva Sadan. Two capsules were given and the bleeding stopped. The patient is continuing normal since then.

Case No. 2: Patient, S.C., aged 16 years, F.M. at 13. Periods were generally in excess. L.M. was continuous for eight days and profuse. One capsule was given on the eighth day at night and the bleeding stopped. This had to be repeated for the second and third month. The patient is continuing normal for six months since then.

Case No. 3: Patient, D.G., aged 14 years, F.M. at 13. L.M. was continuous for ten days, and in excessive quantity. One capsule stopped the bleeding. The patient experienced similar excessive bleeding for three/four months subsequently, and each time it was stopped with one capsule. The patient is having normal periods for eight months, since then.

Case No. 4: Patient, L.B., aged 16 years. Menstrual history was irregular for last eight to nine months. L.M. was profuse for 8-9 days, when three injections of Prolutan produced no results. Two capsules were given for successive days, and the bleeding stopped. The patient is having normal periods for the last six months, since then.

Case No. 5: Patient, M.S., aged 14 years, F.M. at 13. Menstrual history was generally profuse, lasting for about 8 to 10 days. L.M. started with profuse discharge, when on the third day one capsule was given at night, and subsequently 3 more capsules were given within the next 36 hours. Bleeding stopped on the fifth day and the patient became normal. The patient is under observation.

Case No. 6: Patient, A.N., aged 22 years. Married six years. No pregnancy. Menstrual history: menorrhagia 2 years. Profuse and free flow without any clots lasting for 12 to 15 days. Patient had dilatation and curettage done two months back. L.M. with slight bleeding which stopped after two days. Next month the bleeding was profuse, and on the fourth day one capsule was given and the bleeding stopped the next day. The patient is under observation.

Case No. 7: Patient, G.M., aged 32 years. Four pregnancies. Last child seven months old. Menstrual history: Bleeding generally excessive, lasting for 7 to 8 days. L.M. excessive, lasting for 9 to 10 days and attended with

pain. One capsule was given on the tenth day and the bleeding stopped. This treatment had to be repeated for several months and after that, the patient is having normal periods for the last one year.

Case No. 8: Patient, K.R., aged 34 years, F.M. at 15. Three pregnancies. Periods irregular, excessive and painful for the last 1½ years. Periods last for 6 to 8 days and sometimes there is metrorrhagia. On the second day of L.M., one capsule was given and another the next day. Bleeding stopped and the pain disappeared on the fourth day. The next period was regular and without pain. The patient is under observation.

Case No. 9: Patient, R.G., aged 37 years, F.M. at 13. Two pregnancies. Last child 14 years. Periods regular but profuse for the last few years, lasting for 8 to 10 days. Patient becomes anemic after each period, and has to be injected with liver extracts and vitamins etc. during the interval. After examination by a gynecologist, hysterectomy was advised and the patient was removed to Calcutta. Three capsules were administered, one daily from the second day of L.M. Bleeding stopped on the sixth day. Previously she used to pass clots, but this time there were no clots. The patient is under observation.

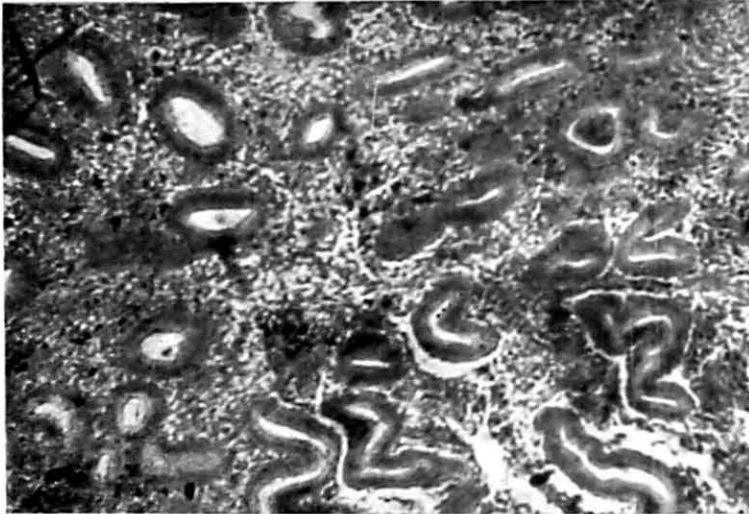
Case No. 10: Patient, B.B., aged 28 years. Three pregnancies, with one abortion. The patient was curetted after abortion. M.H. irregular, painful and excessive bleeding for the last six months and each period lasted for 10 to 12 days and there was also metrorrhagia. According to advice of gynecologists she was again curetted. This curettage has been secured. Bleeding continued after curetting, and she was given two capsules consecutively for two days. The bleeding stopped and the pain disappeared. The next period was normal and without any pain. The patient is under observation.

Case No. 11: Patient, U.G., aged 45 years. Six pregnancies. Last child 7 years. Periods were regular but occasionally profuse. She was given capsules, one every month on the fourth day of the period for the three periods. Since then the patient did not complain of any profuse discharge for the last one year.

Case No. 12: Patient, B.D., aged 42 years. Twelve pregnancies. Last child 9 years. M.H. irregular bleeding for 12 years. Continuous bleeding for the last one month with profuse discharge and the patient became highly anemic. Standard methods of treatment proved ineffective. When two capsules were given, bleeding stopped. The patient was admitted in the Mayo Hospital, Calcutta, where blood transfusion was given and hysterectomy was performed.

Case No. 13: Patient, R.M., aged 40 years. One pregnancy. M.H. Periods were very regular all through. For the last six months, periods were irregular with heavy discharge with menorrhagia and metrorrhagia. L.M. lasted 12 to 14 days. Standard methods of treatment failed when two capsules were given for two days and the bleeding stopped. Next period was normal and lasted only for four days. The patient was examined and malignancy of the cervix was suspected, and the patient is under investigation. Anyway the next period was normal.

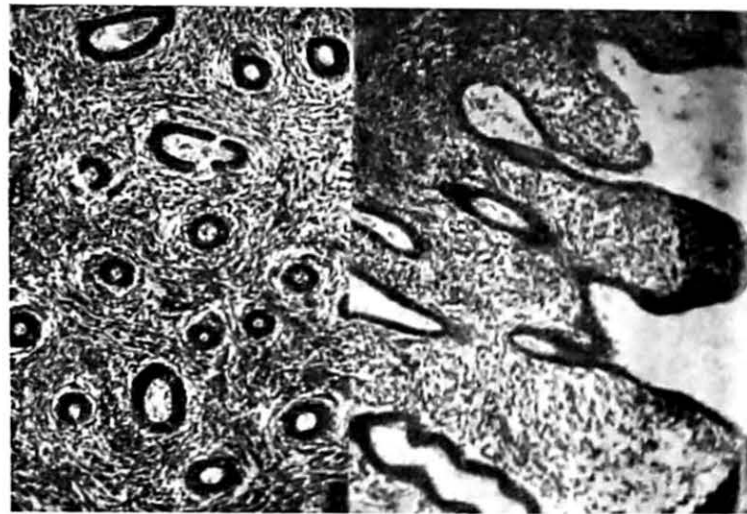
Case No. 14: Patient, Mrs. G., aged 50 years. Nearing menopause. M.H.—periods were irregular for the



CASE No. 1

X 80

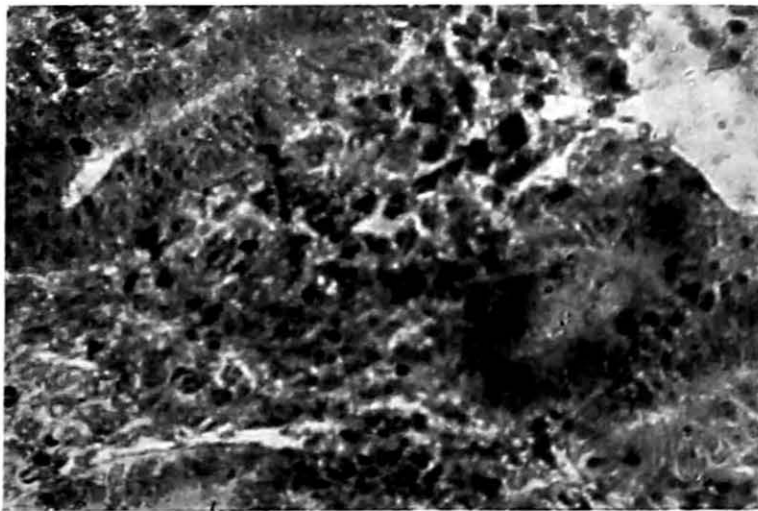
MICROPHOTOGRAPH
OF
ENDOMETRIAL TISSUES



CASE No. 10

X 50

Different sites



CASE No. 1

X 400

last one year or so. L.M. profuse and continuing for 14 to 15 days, when 4 capsules were given in two days and the bleeding stopped. The bleeding recurred again next day and another two capsules were given when bleeding completely stopped and has not recurred since. The patient is under observation.

Endometrial Biopsy Plates

Vide plate attached.

Endometrial Biopsy of Cases 1 and 10 Above

Each section shows evidence of estrogenic manifestation with no evidence of any progestinal phase. Endometrial glands are round and the epithelium showing numerous proliferations. In some cases the glands are all packed with cells. The stroma cells are also dense showing proliferative manifestations. The blood vessels are engorged showing evidence of necrosis in the glands and also thrombosis in the vessels. There is no evidence of "Swiss cheese" at this stage.

Cases Where this Medicine Proved Ineffective

This capsule was tried in other cases of uterine bleeding. Cases of tubercular endometritis, fibroid tumor and endometrial polyp after abortion did not respond even after the administration of 6 to 8 capsules in each case.

Discussion

From the reports of the cases and the results of endometrial biopsy, it is evident that the cases were those of functional bleeding or endometrial hyperplasia, with evidence of monophasic cycle with excess of estrogenic secretion. From the history of the cases and their response to the treatment by m-xylohydroquinone, taken orally in 300 to 350 mg doses, either once or twice daily for one to two days in general, it may be surmised that m-xylohydroquinone can interfere with estrogen or counteract the effect of the estrogen on the endometrium. At this stage however we cannot pronounce its effect on the ovary. This clinical effect is further being corroborated by spectrophotometric study and by biological experiments on rats. This will be the subject matter of a further communication. Here it may also be mentioned that none of the patients complained of any symptom whatsoever. The drug is not at all toxic to the system. The cost of production is very cheap and its effect can be utilised by all classes of people, rich or poor.

Summary and Conclusion

The chemical m-xylohydroquinone which is being used as an oral contraceptive in a large number of human trial cases, has been found to be effective in functional bleeding. This effectiveness is in all probability due to the fact that it can interfere with the estrogens or counteract the effect of estrogens on the endometrium.

Records of fourteen cases have been discussed and microphotograph of the endometrial tissue sections of two cases have been depicted.

Acknowledgments

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ORIGINAL COMMUNICATIONS

FURTHER CLINICAL RESULTS WITH METAXYLOHYDROQUINONE
AS AN ORAL CONTRACEPTIVE

By S. N. Sanyal, B.Sc., M.B., and (Mrs.) S. Ghosh, M.B., L.M., D.G.O.
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The finding of Professor N. C. Nag that the feeding of the seeds of *Pisum Sativum*, Linn to rats greatly reduced their production of offspring¹ led to the testing of an oil extracted from the seeds as a monthly intramuscular injection for women.² When this proved successful in postponing pregnancy, the active principle was isolated and its chemical nature was determined to be m-xylohydroquinone. When this compound was tested on rats, along with its four analogs, m-xylohydroquinone was found to be most protective and least toxic.³ In ovariectomized rats it prevented an increase in the weight of the uterus and also the development of the endometrial glands after the administration of progesterone. It was thought, therefore, that it would be most effective if administered shortly before the menstrual period.

For a clinical test the metaxylohydroquinone was prepared from meta-xylydene (2,6 dimethyl aniline) secured from Distillation Products Inc. a subsidiary of the Eastman Kodak Company. This was converted to the hydroquinone in two stages. It was first oxidized with chromic acid and the quinone formed was simultaneously distilled off by steam. The quinone was extracted with benzene and the benzene solution of quinone was reduced with aqueous hydrosulphite, yielding about 60-70 per cent of meta-xylohydroquinone.

To prevent oxidation of the meta-xylohydroquinone in the intestine, it is administered in capsules together with 5 per cent of its weight of sodium hydrosulfite and 10 per cent of dextrose.

In a previous report pregnancy rates were given of 268 patients taking a capsule of the compound twice each month over a total of 825 months. It was found that the rate which had been 62 per 100 couples per non-pregnant year was reduced to 31. When the first two months of each user's experience and the pregnancies arising therein were disregarded the rate was 17. To increase the accuracy of the results these patients have been continued over longer periods, and new ones enlisted. The results are given herewith.

To many of the patients, because of the distance of their homes from the hospital, one or both of the capsules were given to be taken at their homes. Since there was no certainty that the capsules were taken or were taken on the prescribed day, a SECOND SERIES of patients was enlisted. These were secured by visiting homes in the underprivileged areas close to the Baldeodas Maternity

Hospital in Calcutta, offering the capsules without cost. The health visitor observed and recorded the swallowing of each capsule. The results of this series are also given in the Table.

Pre-medication Pregnancy Rates

The number of pregnancies per 100 couples per non-pregnant year was calculated for each group. From the total years of married life there were subtracted $\frac{1}{4}$ year for each live-birth or stillbirth, and $\frac{1}{2}$ year for each miscarriage. The total number of pregnancies \times 100 was then divided by the net number of non-pregnant married years.

As Table I shows, the pregnancy rate for each series was 65 per 100 couples per year. That the desire for protection from pregnancy was strong was suggested by the fact that the average number of previous pregnancies had been six.

Medication

During the first four months of the FIRST SERIES (which began in June, 1953) one capsule containing 150 mg. of metaxylohydroquinone was administered orally each month about 8 to 10 days before the expected onset of the next menstrual period. From the fifth to the 12th month of the First Series two such capsules were given each month. Subsequently in the First Series and throughout the Second Series (which began on April 1954) two capsules were given each month, each containing 300 to 350 mg. meta-xylohydroquinone.

The time of administration was chosen with the expectation of preventing the lining of the uterus from being prepared for nidation. Laterly the two doses in both the Series were given on the 16th and 21st day of the cycle, but initially in the First Series the chosen days were the 12th and 7th day before the expected onset of the next menstruation, assuming that the interval would be the same as the previous one. To patients who were not menstruating a capsule was given every fortnight approximately.

In the First Series the patients were instructed to visit the clinic on the appropriate day, when one capsule was administered personally by the health visitor. The other capsule was given to the patient with instructions as to when to take it. If the patient did not appear on the correct day a reminding postcard was sent, but as most of the patients were illiterate these reminders were not very effective. In addition some visits were made to the homes of those who did not return.

To the patients in the Second Series the capsules were administered in their homes by the Health Visitor, and

Read at the Fifth International Conference on Family Planning in Tokyo, October, 1955.

recorded on the history. With each patient was left a post-card addressed to the Hospital for the reporting of the date of the next menstrual period. Receipt of this post-card permitted the worker to calculate the duration of the period. Assuming that the next period would be of the same number of days, the 16th and 21st days were then determined. To avoid excessive travel the Health Visitor went to homes east and west of the Hospital on alternate days, and the administration was delayed one day if necessary to meet this schedule.

Pregnancy Rates during Medication

The number of patients continuing the medication for a given number of months, and the number of pregnancies occurring in each group are shown in Table 2. Months in which medication was not given have not been included in the numbers given. There were 236 such months without medication in the First Series and 59 in the Second Series. There were 8 pregnancies which followed these omissions in the First Series occurring, one each in the 2nd, 4th, 7th and 8th month of administration and two each in the 3rd and 5th month. In the Second Series there were 3 pregnancies following omissions—one in the 2nd and two in the third month. These pregnancies have not been included in the calculations. The oral method of contraception, as used, has the advantage over other birth control methods that the months in which no medication is taken are known without doubt to those providing the medicine and (except for possible errors in estimating the date of conception) the resulting pregnancies can be accurately attributed to them.

Pregnancies which a careful physical examination showed to have existed before the medication was begun have not been included in the calculations. The numbers of these are indicated in the table.

For each series the total number of months of use has been determined by multiplying the number of patients in each group by the months used and adding together all the products. The pregnancies per 100 couples per year was then calculated by the formula:

$$(\text{Pregnancies} \times 1200 / \text{total months.})$$

In the first series 427 patients took the compound for 2167 patient-months and had 56 pregnancies. The pregnancy rate was 31 per 100 couples per year.

It is often difficult to determine whether a pregnancy occurring early in the time of medication existed before the compound was taken. More accurate results can, therefore, be secured if pregnancies discovered in the first two months are omitted, together with the first two months of every patient. For the First Series the pregnancy rate for 285 patients with 1387 patient months for the third and subsequent months, calculated in this way is 27 per 100 couples per year.

For the Second Series, the pregnancy rate for 254 couples with a total experience of 1465 months was 20. When only the third and later months are considered, 179 couples taking the medication with 1025 patient-months had a rate of 11 per 100 couples per year. This corresponds to a pregnancy every 9 years. While this is encouraging, it is desirable for greater accuracy in measuring the protection to continue the study, including a larger number of patients over times which should be measured for each in years, rather than months.

The Effect of Postpartum Amenorrhea

As many of the patients were enlisted at a maternity hospital the proportion with postpartum amenorrhea may be somewhat higher than that of the average Indian population. To determine the results when this partially protective factor was absent, the pregnancy rates were re-calculated for the time beginning at the first recorded menstruation. The results are given in Table 2. It will be seen that the rate is 37, per 100 couples per year for first series, somewhat higher than that of 31 when all months are included in the calculation. As menstruation is apt to be irregular when it is first re-established, with the result that the medication may not be given at the intended interval before the next menstruation, the rate was also calculated after the omission of the first two months for each menstruating patient. The rate found was 32 per 100 couples per year.

Similar calculations for the menstruating patients of the second series, in which the taking of the capsules was observed, showed a pregnancy rate of 27 for the entire time, somewhat higher than that of 20 when the non-menstruating patients were included. When the first two months of each patient's experience were disregarded, the rate was 12, almost the same as the rate of 11 found for all the patients. This suggests that postpartum irregularities in menstruation may have been the cause of some of the pregnancies, and that the exact timing of administration may be important.

Evidence against Abortifacient Action

During the study 46 patients in the First Series and 22 in the Second Series were found to have been pregnant before taking the first capsule. Although they took capsules for from one to four months, not recognizing or concealing their pregnancy, no abortion occurred.

No Evidence of Injury to Fetus

To determine whether metaxylohydroquinone might have an effect on the baby, patients who became pregnant were encouraged to come to the hospital for confinement. Of the 32 such cases delivered at the hospital who had taken the compound, 27 had normal babies without deformity. These weighed from 5 to 8 pounds. Of the remaining patients 2 had stillbirths, each 7 months after the last capsule. The history of one of these records asphyxia as the probable cause of death. The 3 other patients had abortions, 2, 4, and 7 months after the last capsule. Each gave a history of one or two previous abortions.

It seems improbable that the metaxylohydroquinone would cause damage to the fetus which would result in termination of pregnancy so long after its administration.

Sterility is not Permanent

That permanent sterility does not result from the use of metaxylohydroquinone is shown by the 8 conceptions in the first series following omissions in 236 months and 3 conceptions in the second series after omissions in 59 months. In July 1955, it was possible to find 33 others living near the hospital who had discontinued the medication after taking it for an average period of 8 months. Of these 8 (average medication 6 months) had become pregnant.

According to the patient's estimate of the duration of the pregnancies 2 of these began in the first month, 3 in

the second, 3 in the third and 1 in the fifth month. For the 25 non-pregnant women in this group, the average time since discontinuance had been 3.6 months. While the number of those who could be found and who had discontinued the medication was small, and the time since discontinuance short, there is no indication that sterility had resulted.

No Toxicity Detected

No patient has complained of any toxic symptoms except for a negligible few who told of some griping in the abdomen if the capsule was taken on an empty stomach.

A search was made for the possible development of evidence of toxicity over a period of prolonged use of the compound. Eighty patients who had been taking two monthly doses of 150 to 300 mg. each of metaxylohydroquinone for from 9 to 21 months (average 12 months) were examined, and the results compared with those of 63 newly enlisted users from the same economic group who had not taken the compound.⁴ No significant differences were found between averages for the two groups of blood pressure, pulse rate, hemoglobin, red-cell count, white-cell count, differential white cell count or albumin or casts in the urine. It was concluded that there was no evidence of cumulative toxicity over the period in question.

Timing and Size of Doses

In the First Series, in most instances, the swallowing of the first capsule was observed, and was known to have occurred on approximately the 16th day from the date of menstruation. The difference between the two Series lies chiefly in the uncertainty of taking and timing of the second capsule, which was observed by the Health Visitor only in the Second Series, but for the most part was not observed in the First Series. It is possible, therefore, that the markedly higher pregnancy rate found in the First Series arose chiefly from failure to take the second capsule or to take it on the recommended day. If this assumption is correct it indicates that full protection is not given from a single dose as early as the 12th premenstrual day.

The lesser protection secured in the First Series also suggests that a method depending upon medication once or twice a month may not be fully successful in a group such as that tested, one which was chiefly illiterate and unfamiliar with accurately timed procedures. It may be that more frequent doses, perhaps once each week will be more apt to be taken at the needed time and consequently more effective in such groups.

It is also possible greater protection may be secured by more frequent doses during the premenstrual period, but this has not yet been explored. If further tests show that protection is possible with a single dose each month, the method will be better adapted to groups in which it is found that calculation and reminding of dates by a health visitor is needed to assure administration at the correct time.

No evidence is yet available to show the minimum size of dose needed for protection. After a procedure has been found which gives satisfactory protection, simplification and reduction of dosage can be tested.

A Proposal for Further Study of the Clinical Effect of Metaxylohydroquinone

After a review of the preliminary report⁵ and a detailed study of a sample of the records of the cases here sum-

marized, Dr. C. Chandrasekaran and Dr. (Mrs.) Mukth Sen of the All-India Institute of Hygiene and Public Health, Calcutta, have proposed to the Government of India an appropriation under the Research Programme in Family Planning, included in the Five-Year Plan, to continue the study of this use of meta-xylohydroquinone in addition to a continuation of the clinical study for one or three years they suggest further toxicity tests and biological investigations to determine more accurately the physiological mechanism through which the protection from pregnancy is secured.

Recently news has been received from the Director General of Health Services that the proposal has been accepted by the Government of India.

The Cost of Protection

2,6 dimethyl aniline is sold by Eastman Kodak Co. for \$14.50 (Rs. 70) for 500 grams. This will produce about 300 grams of metaxylohydroquinone. For the 24 capsules needed for a year's treatment, the raw-material cost will therefore, be about Rs. 2 (40 cents). To this must be added the expense of shipping, chemical processing, mixing with the sodium hydro-sulfite and glucose (of which the cost is negligible), placing in the capsules and delivering to the patient. In the First Series medication of 10 couples per year was followed by 34 fewer pregnancies than there would have been at the previous rate, and in the

TABLE 1—Pregnancies Before Medication

	First Series	Second Series
Patients	473	254
Live Births	2,606	1,411
Stillbirths	59	30
Miscarriages	176	144
Total Pregnancies	2,841	1,585
Married Years	6,448	3,588
Non-Pregnant Years	4,384	2,454
Pregnancies per 100 Couples per year	65	65
Pregnancies per couple	6.0	6.2

TABLE 2—Pregnancies During Medication
First Series

Months of use	Including Months of Amenorrhoea			Excluding Months of Amenorrhoea		
	Patients	Patient Months	Pregnancies	Patients	Patient Months	Pregnancies
24	1	24	0	1	24	0
21	1	21	0	1	21	0
20	2	40	0	2	40	0
19	3	57	0	1	19	0
18	3	54	0	2	36	0
17	1	17	0	2	34	0
15	5	75	1	2	30	0
14	3	42	1	3	42	1
13	3	39	0	2	26	0
12	10	120	2	10	120	2
11	2	22	0	3	33	1
10	13	130	2	6	60	0
9	14	126	3	10	90	1
8	30	240	5	16	128	5

	Including Months of Amenorrhoea			Excluding Months of Amenorrhoea		
	Months of use	Patient Months	Pregnancies	Patient Months	Pregnancies	Pregnancies
7	37	259	1	24	168	3
6	28	168	1	19	114	0
5	45	225	6	27	135	5
4	46	184	5	38	152	4
3	38	114	4	34	102	4
Subtotal	285	1,957	31	203	1,374	26
2	68	136	18	60	120	14
1	74	74	7	73	73	8
Subtotal	427	2,167	56	336	1,567	48
Preg. before use	46	0	0	46	0	0
No menstruation	91	0	0
TOTAL	473	2,167	56	473	1,567	48
Pregnancy rate:						
All months	31	37
Omitting first two months	27	32

Second Series

	Including Months of Amenorrhoea			Excluding Months of Amenorrhoea		
	Months of use	Patient Months	Pregnancies	Patient Months	Pregnancies	Pregnancies
15	5	75	0	3	45	0
14	4	56	0	3	42	0
13	5	65	0	3	39	0
12	10	120	0	4	48	0
11	8	88	0	5	55	0
10	15	150	0	7	70	0
9	21	189	2	8	72	1
8	20	160	2	15	120	2
7	22	154	0	14	98	0
6	25	150	0	16	96	0
5	14	70	2	13	65	1
4	16	64	1	12	48	0
3	14	42	2	17	51	2
Subtotal	179	1,383	9	120	849	6
2	29	58	11	20	40	9
1	24	24	4	45	45	6
Subtotal	232	1,465	24	185	934	21
Preg. before use	22	22
No menstruation	47
TOTAL	254	1,465	24	254	934	21
Pregnancy rate:						
All months	20	27
Omitting first two months	11	12

Second Series by 45. The raw-material cost will, therefore, be approximately Rs. 6 (\$ 1.25) and Rs. 4-8 (95 cents) respectively, for the two series, for each pregnancy prevented.

For those in the second series, the cost of distributing the capsules and observing the swallowing must be included. An estimate of this may be made from the fact that one health visitor is now taking the capsules twice each month to about 200 families, as well as using some of her time to offer the service to new ones. The cost of the health visitor's salary is approximately Rs. 6 (\$ 1.25) for each patient per year, or Rs. 24 (\$ 5) and for each undesired pregnancy prevented.

The expenses appear, therefore, well within those possible in a public health program, and are probably less for each pregnancy prevented than the cost of the obstetrical service offered in many Indian cities.

Summary

When meta-xylohydroquinone in doses of 300 to 350 mg. was taken by mouth by women, twice each month on the 16th and 21st day of menstruation, the pregnancy rate decreased. Among those allowed to take the second dose at home the pregnancy rate was reduced by 52 per cent (rate 31 per 100 couples per year). When both capsules were taken to the patient and the swallowing observed, the reduction was 69 per cent (rate 20), and when, in addition, only the third and later months were considered the reduction was 83 per cent (rate 11).

When periods of postpartum amenorrhoea were omitted, the rates were 37 for those allowed to take the capsules at home and 27 for those who swallowed the capsules in the presence of the worker. For the latter group, the rate was 32 1st series, 12 second series, when only the third and later months were considered.

Continuation of the medication during pregnancy did not result in abortion.

27 live babies born to mothers who had taken the compound were all found to be normal and without deformity.

Among 33 who had discontinued medication, 8 conceived within three months.

No immediate or cumulative toxicity of the drug has been found.

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ORIGINAL COMMUNICATIONS

PISUM SATIVUM (LINN) :
TOXICITY TEST OF m-XYLOHYDROQUINONE WHEN USED AS AN ORAL CONTRACEPTIVE

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m-Xylohydroquinone, which is being used as an oral contraceptive by quite a large number of women patients, is showing very encouraging results. The dosage is only 300 to 350 mg. taken orally twice a month. The attendance of voluntary patients at the clinic is gradually increasing. A large number of private patients, about 800 in number, have taken and are taking the medicine for various periods and no undesirable effects have as yet been reported. Had there been any such effects, the number of voluntary patients would certainly have decreased rapidly. It is apparent that the medicine has no toxic effect on the human system. Still doubts have been expressed in some quarters as to its possible cumulative toxic effects when used for prolonged periods. For a scientific answer to this, the present work was undertaken at the instance of Dr. CLARENCE J. GAMBLE, M.D. of Boston, Mass., U.S.A.

Toxic effect of a drug, if acute, is always demonstrated by immediate symptoms such as nausea, vomiting, giddiness, acute pain, anuria, diarrhoea, fainting etc. If the effect is chronic, it is expected to be reflected in the pulse rate, rise or fall of blood pressure, loss of hemoglobin, diminution of total number of red blood corpuscles in the blood and also abnormal changes in the white blood corpuscles. Albumin and casts are also expected to appear in the urine as a result of kidney damage. In the evaluation of m-Xylohydroquinone taken orally, no acute symptoms were encountered in the trial with such a large number of patients, who were using the medicine twice every month even upto 24 months or so. Now it remains to determine whether there is any change in the system of the subjects who are using the medicine for a prolonged period.

In the determination of toxicity in the human trial, the usual procedure should be to determine the level of pulse rate, blood pressure, blood count, hemoglobin estimation, etc., in each subject prior to the administration of the medicine in the beginning and subsequently at different periods during the course of the administration of the medicine. If there be any abnormal deviation in the subsequent examination results against that of the first group, it may be taken to be due to the effect of the drug. But there may be an objection against the incorporation of an unknown and very variable factor namely TIME. During the period of use many unknown or rather unmeasurable changes caused by economic or mental factors, may take place which alone can be responsible for such symptoms. Only gross physical changes such as physical injury or any intercurrent or intervening illness are detectable and are expressed without hesitation.

In cases, affected by personal misfortune, or mental strain, psychological imbalance or serious economic trouble etc. the deviation may not express the true picture of the effect of the drug alone. To counteract this the following procedure was adopted.

Method

The clinical examination of pulse rate, blood pressure, hemoglobin in grams and in per cent (SAHLI), total R.B.C., W.B.C., differential count of white cells, albumin and casts in urine etc., were estimated for a group of control cases who had just enrolled themselves at the clinic and had not taken any contraceptive capsules. The statistical mean was determined for each item. Similar examinations were also done for each patient volunteer who have taken the medicine for nine months or over. Here also the statistical mean was determined for each item. If there was any apparent deviation, "t" *i.e.* treatment variance was to have been determined at 1 per cent or 5 per cent level just to find out whether the variation was significant or not. In a complex biological system it will be unwise to pronounce a judgment for any apparent change unless and until it is shown to be statistically significant.

In the present trial both the groups—control and the treated—came from the same strata of society, namely the lower middle class and were of the same economic level. This has been adequately proved from their blood-pressure and hemoglobin contents.

It is to be regretted that volunteers for such observations were not easy to obtain. There was a great deal of difficulty in inducing them to submit to clinical examinations of blood, urine, etc. Due to ignorance they were always suspicious of such procedure. Still however 63 control cases could be examined and these were as far as practicable consecutive cases without any selection. Similarly 80 treated cases were examined and these were only those who volunteered. No patient in this group, was entertained who did not use the medicine for at least nine months.

Analysis of the Results

Before giving the statistical average, the general analysis of the cases of both the series are described below.

STATISTICAL REPORT

When compared, the results agree so much between the two groups that the determination of "t" is not required, *i.e.*, there is no variation at all. The number of samples in each group is sufficiently high to give results which are significant.

	Maximum Observed	Minimum Observed	Rest
(A) CONTROL GROUP: Total of 63 cases.			
Blood Pressure (mm. Hg.)	140/100 three cases; 130/80 two cases	90/60	100/70 to 120/90
Pulse Rate (per minute)	100	72	80 to 90
Hemoglobin* (Gm./100 c.c.)	10.9 (75%)	7.5 (52%)	8.5 to 9.5
Total R.B.C. (Millions)	4.63	3.19	
Eosinophils	23%	1%	
Albumin	Trace—33 cases; Distinct but not estimable—one case		
Casts	Found in no case		
(B) TREATED GROUP: Total of 80 cases.			
Blood Pressure† (mm. Hg.)	190/110 one case; 140/80 three cases; 130/80 three cases;	90/60	100/70 to 120/80
Pulse Rate (per minute)	90	62	
Hemoglobin (Gm./100 c.c.)	12.4 (84%)	9.0 Gm. (62%)	
Total R.B.C. (Millions)	4.45	3.47	
Eosinophils	21%	1%	
Albumin	Trace only— 10 cases; Distinct but not estimable—no case		

* Hemoglobin:—Normal: 14.5 Gm. equals 100 per cent.

† This patient was suffering from symptoms of high blood pressure. On interrogation she informed that the use of the medicine did not improve the symptoms, nor was she worse in any way.

Months of use:—TREATED GROUP: Maximum: 21 months; Minimum: 9 months. CONTROL GROUP: Maximum and Minimum: nil.

STATISTICAL REPORT

	Control Group Mean S.D.	Treated Group Mean S.D.
Total Number	63	80
Age	28.9 ± 6.40	31.1 ± 6.05
Conceptions	6.3 ± 2.76	6.6 ± 2.92
Months of Use	nil	12 months
Blood Pressure	111 ± 11.20 76 ± 6.90	114 ± 13.06 77 ± 8.05
Pulse Rate	84 ± 5.50	84 ± 5.80
Hemoglobin (Gm./100 c.c.)	9.6 ± 0.74 (67% ± 6.50)	10.1 ± 0.53 (70% ± 0.70)
Total R.B.C. (millions)	4.03 ± 0.33	4.09 ± 0.26
Total W.B.C.	6563 ± 280.00	6576 ± 720.00
Polymorphs (%)	57.8 ± 9.15	59 ± 8.55
Lymphocytes (%)	32.2 ± 8.50	32 ± 8.40
Monocytes (%)	2.5 ± 0.50	2 ± 0.50
Eosinophils (%)	7.52 ± 6.30	7 ± 4.50
Casts	none	none

Discussion

From the above observations two facts become fore-ent. Hemoglobin level is too low in both series. This distinctly indicates the lower economic level to which both the groups belonged. Secondly the pulse rate is high, namely 84. This seems to be due to a low diet and also perhaps to strain of walking a distance in hurry to reach the Clinic in time. The percentage of eosinophilis is higher than usual, in both the series. This is rather difficult to account for.

From the analysis of the cases and also the finding of the statistical mean of the clinical examination results of the two series—control and the treated cases—it may be concluded that the drug m-Xylohydroquinone which is being used as an oral contraceptive in 300 to 350 mg. doses twice a month, is not at all toxic to the human system. Further it may be said that m-Xylohydroquinone which is an anti-vitamin-E, cannot fully counteract the effect of vitamin-E in the system. The total storage of this vitamin in the human system such as liver, muscle, heart and other organs is so much that it is never possible to neutralise the whole of it. Further it is being constantly replenished from normal food. It is only possible to avitaminise rats whose store of vitamin-E is rather poor and its supply is greatly dependant on the food intake.

Summary and Conclusions

The clinical examination results of blood pressure, pulse rate, hemoglobin, total red blood cells, white blood cells, differential count, and albumin and casts in urine of 63 control cases and 80 treated cases have been described. The statistical mean of each item in the two groups agree fully.

All these definitely prove that m-Xylohydroquinone, is not at all toxic to the human system.

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