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ACTION OF METHALLENOESTRIL ON THE POST-MENOPAUSAL ENDOMETRIUM AND VAGINAL EPITHELIUM

A COMPARATIVE STUDY

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Methallenoestril ("vallestril") is a phenolic acid derived from naphthalene that has been shown to be more strongly oestrogenic than oestradiol when administered parenterally in oily solution to castrated female rats (Courrier, Horeau, and Jacques, 1947). It has the descriptive formula 3-(6-methoxy-2-naphthyl)-2,2-dimethylpentanoic acid. It is relatively insoluble in water and gastric contents, but soluble in alcohol, in oil, and in dilute bases such as occur in the intestinal secretions. Sturnick and Gargill (1952) have found methallenoestril to be effective in the control of "menopausal symptoms" and of the pain of post-menopausal osteoporosis, without causing uterine bleeding during treatment or after withdrawal.

Potency studies in the laboratories of the manufacturers have shown that, while the oestrogenic effect of methallenoestril on the vaginal epithelium of spayed mature rats is twice that of oestrone, its influence on uterine growth in immature mice is only one-tenth as potent as that of oestrone. The present investigation was undertaken to determine whether this selective oestrogenic action of methallenoestril was demonstrable in women, and this was done by comparing its action on the endometrium and vaginal epithelium with that of stilboestrol.

The subjects of the investigation were patients awaiting vaginal repair operations for genital prolapse in whom the menopause had occurred five or more years previously. Each of these was given a course of tablets labelled A, B, or C, the nature of which was unknown to the investigators until the study was complete. The course of tablets, one a day, was given for a period of between 40 and 84 days, and the interval between completion of the course and endometrial curettage at the time of the vaginal repair operation was between 4 and 15 days.

The tablets labelled A contained 5 mg. of methallenoestril, those labelled B were inert, and those labelled C contained 0.5 mg. of stilboestrol.

Results

It may be seen from the Table that of the seven patients who received methallenoestril only one experienced withdrawal bleeding. This patient and one other were found to have hyperplastic endometrium. Of the 10 patients in the control group not one had withdrawal bleeding, although in three cases endometrial polypi were found, and in two of these the endometrium was relatively hyperplastic for a post-menopausal woman. Of the eight patients who received stilboestrol, four experienced withdrawal bleeding only, one induced bleeding, and one both induced and withdrawal bleeding. All of these, together with a seventh who did not bleed, were found to have hyperplastic endometrium. One patient had an endometrial polyp.

The diagnosis of "hyperplastic endometrium" was made on the basis of a naked-eye judgment of the amount and thickness of the endometrium confirmed by microscopical evidence of active proliferation or frank cystic hyperplasia. The four endometrial polypi (of which three occurred in the control group) were discrete adenomata arising by slender pedicles within the uterine cavity. They were considered to be innocent neoplasms rather than manifestations of hyperplasia.

The condition of the vagina was compared by noting the presence or otherwise of obvious atrophic changes in the epithelium. This was present in one of the seven methallenoestril cases, five of the 10 controls, and none of the eight stilboestrol cases.

Five patients volunteered the information that they felt better in general health and that their symptoms of prolapse were moderated after taking the tablets. Of these, three received methallenoestril and two the inert tablets.

Tabulated Results

	Age	Years since Menopause	Days of Treatment	Interval before Curettage (Days)	Induced Bleeding	Withdrawal Bleeding	Atrophic Vaginitis	Endometrium		
								None or Scanty	Hyperplastic	Polyp
A. Methallen- oestril										
2117/56	68	16	49	10	—	—	—	—	+	—
30661/54	65	15	63	15	—	—	—	—	—	—
46285/54	62	12	42	10	—	—	—	—	—	—
11174/56	62	10	42	10	—	—	—	—	—	—
13164/54	61	10	46	4	—	—	—	—	—	—
25128/55	58	10	62	10	—	—	—	—	—	—
10982/56	57	5	42	10	—	+	—	—	+	—
B. Control										
26697/54	59	18	44	10	—	—	—	—	+	—
27838/52	56	14	41	10	—	—	—	—	—	—
11349/50	63	11	42	10	—	—	—	—	—	—
2800/49	57	8	43	10	—	—	—	—	+	—
21632/55	57	7	42	10	—	—	—	—	—	+
10316/55	59	5	44	8	—	—	—	—	+	—
392/57	55	7	63	10	—	—	—	—	—	+
5072/57	46	5	73	10	—	—	—	—	+	—
40193/56	59	10	84	10	—	—	—	—	—	—
27136/52	57	5	84	10	—	—	+	—	+	—
C. Stilboes- trol										
35248/53	59	19	40	10	—	—	—	—	+	—
925/49	57	9	44	8	+	—	—	—	+	—
373/56	57	7	41	10	—	—	—	—	+	—
4351/56	57	7	41	10	—	—	—	—	+	+
38570/56	66	14	69	10	—	—	—	—	—	—
23902/56	61	11	68	10	—	—	—	—	+	—
44359/49	61	8	63	13	+	+	—	—	+	—
18427/56	66	16	82	10	—	+	—	—	+	—

Summary

A "double blind" trial of methallenoestril (vallestril) and stilboestrol has been carried out on 25 post-menopausal women awaiting vaginal repair operations.

Abnormal bleeding occurred in six out of eight patients who received stilboestrol and in only one of

the seven patients who received methallenoestril. Both macroscopic and microscopical examination of the endometrium has shown a lesser degree of oestrogenic stimulation in those who were given methallenoestril. The results may be largely explained by the fact that methallenoestril is a weaker oestrogen than stilboestrol, but there is some evidence of a selective action by the former which would make it a more suitable preparation for the treatment of post-menopausal vaginitis, post-menopausal osteoporosis, and the symptoms of the climacteric. A healthy vaginal epithelium was observed in all eight of the patients treated with stilboestrol, and all except one of the seven who were given methallenoestril. Five of the 10 controls had obvious atrophic changes.

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A UNIQUE CASE OF AUTO-IMMUNE ERYTHROCYTE SENSITIZATION

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Occasionally the red blood cells of an apparently normal person will be found to have a positive reaction when a direct anti-globulin test is carried out. Usually this can be demonstrated to be a "false positive" due to *in vitro* sensitization with the normal cold incomplete antibody. Very rarely is a true positive reaction found in healthy people (Dacie, 1950, 1954). Little has been written on this aspect of the antiglobulin test, and the occurrence in a blood donor of a true positive direct antiglobulin reaction must be very unusual.

Mr. X, group A₁, Rh genotype cde/cde, has given 26 donations of blood since 1941, and since 1948 has attended donor sessions regularly twice or three times each year. No trouble was experienced until his 25th donation in October, 1957. The hospital laboratory, selecting blood for one of their "dangerous" recipients, included an indirect antiglobulin test as well as saline and albumin techniques in the compatibility tests. Mr. X's blood was found to be "incompatible" by the indirect antiglobulin test, but compatible in saline and albumin media. As is the custom, this bottle of blood and the patient's serum were sent to us for investigation, when the donor's blood was found to give a moderately strong positive direct antiglobulin reaction, agglutinates appearing in about one minute. The patient's serum contained no antibodies. The apparent incompatibility on cross-matching was thus explained.

A direct antiglobulin test using serial dilutions of the reagent gave the results shown in Tables I and II. This gave the first surprise. The optimum reactions with Mr. X's cells were in the same range as the optimum for Rh (anti-D) sensitized cells suggesting a "warm" antibody was coating the cells. Inhibition of the reactions with γ -globulin showed the coating antibody was of the γ -globulin type—further confirmation that a "warm" type sensitizing antibody was involved. The second surprise came when a red-cell eluate prepared by Weiner's (1957) method was tested against a

panel of cells of known phenotype and was found to contain the specific auto-antibody anti- $\bar{c}$. This was demonstrable by the indirect anti-globulin technique, but not in saline or albumin.

No abnormal antibodies were found in the serum. Tested against a panel of R.B.C.s, no abnormal agglutinins were present apart from a very weak auto- and pan-agglutinin demonstrable at 4° C. only. Neither cold nor warm haemolysins were detected. The Donath-Landsteiner reaction was negative.

The serological findings were those usually associated with a moderately severe haemolytic anaemia.

The haematological findings on January 25, 1958, were as follows: Hb, 92% (13.6 g./100 ml.); R.B.C., 4,510,000 c.mm.; reticulocytes, less than 1%; W.B.C., 4,000 (polymorphs 52%, eosinophils 2%, lymphocytes 40%, monocytes, 6%). R.B.C.s and W.B.C.s apparently normal; platelets, 275,000. Hess test negative. Bleeding- and clotting-times normal. Prothrombin time normal. Red-cell saline fragility—within normal limits. No abnormalities were present, nor were any found on physical examination.

Past medical history included a hernia repair in 1939 and removal of a cartilage from a knee-joint in 1956. No history of any significant illness was given. Particular inquiry into any possible virus infection was made. He has never had a blood transfusion.

In March, 1958, a further donation was taken and the extensive serological tests were repeated. The direct anti-globulin reaction was still positive, and the pattern of the reaction was identical with that previously found. An eluate prepared from the red-cell stroma no longer had an anti- $\bar{c}$ specificity, having broadened its activity and now being, so-called, non-specific.

Dr. W. Weiner has completely confirmed the later serological findings and had some additional investigations done on the serum. Ultracentrifugal analysis gave perfectly normal results. A haptoglobulin estimation showed these to be definitely deficient, having a level only 50% of normal.

The fate of the man's blood donations since 1952 was investigated by inquiry of the hospitals using them. A particular point was made of asking whether any difficulty had been experienced in performing compatibility tests, particularly when the indirect anti-globulin technique had been used. The most recent occasion when the indirect antiglobulin test was used in a compatibility test was in November, 1955, and this was negative. Knowing that, using a single-dilution antiglobulin test, a positive reaction would have been obtained if present, there is no reason to doubt that in 1955 this donor's erythrocytes were normal. An antiglobulin test was not done on these cells again until the start of this investigation in November, 1957; the present state of autosensitization has therefore developed within the last two years.

TABLE I.—Direct Antiglobulin Test

Final Dilutions of A.H.G.	4	8	16	32	64	128	256	512	1,000	2,000
Mr. X	w	w	w	(+)	+	++	++	++	+	+
Rh-positive cells, sensitized with anti-D	++	++	++	++	++	+++	+++	+++	++	+
Rh-positive cells, unsensitized	+	w	—	—	—	—	—	—	—	—

TABLE II.—Direct Antiglobulin Test after Adding an Equal Volume of 1/400 γ -globulin to each Dilution of A.H.G.

Final Dilutions of A.H.G.	4	8	16	32	64	128	256	512	1,000	2,000
Mr. X	—	—	—	—	—	—	—	—	—	—
Rh-positive cells, sensitized with anti-D	(+)	(+)	?	—	—	—	—	—	—	—
Rh-positive cells, unsensitized	(+)	?	—	—	—	—	—	—	—	—