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.

We wish to thank Mr. Victor Lack, Mr. Alan Brews, and Mr. Robert Percival for permission to treat their patients and for their encouragement. The tablets for the investigation were prepared by G. D. Searle and Co.

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A UNIQUE CASE OF AUTO-IMMUNE ERYTHROCYTE SENSITIZATION

BY

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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	(+)	?	—	—	—	—	—	—	—	—

Mr. X is 44 years old and is a coal-miner working at the coal face. He has no complaints whatsoever. He has two abnormalities—a positive direct antiglobulin reaction and a low haptoglobulin level. An apparently healthy man with this type of true positive direct antiglobulin reaction and no significant previous illness seems to be unique.

This case obviously needs following before a final answer to the present finding can be given. The most likely explanation is that he has an acquired haemolytic "anaemia" which has been detected in a very early stage, and which is at present fully compensated, although one might have expected a higher reticulocyte count. The low haptoglobulins suggest that haemolysis may be active. Nosslin and Nyman (1958) found these levels to be low in haemolytic diseases. The serological findings are those of a haemolytic anaemia; the haematological findings are normal. The picture is very similar to that sometimes seen in known cases of acquired haemolytic anaemia, either during natural remission or after treatment with steroids or by splenectomy. It remains to be seen whether in the course of months or years the present findings will change and show the full picture of an acquired haemolytic anaemia.

A further examination of specimens taken in October, 1958, showed no change. The haemoglobin level was normal and the red cells still showed the same degree of sensitization.

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BILATERAL THROMBOPHLEBITIS AFTER A SINGLE DOSE OF ERGOTAMINE TARTRATE FOR MIGRAINE

BY

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Although ergotamine tartrate has such a well-established place in the treatment of the acute attack of migraine and the toxic effects of ergot and its alkaloids are so often quoted, the incidence of thrombophlebitis occurring after ergotamine tartrate has not often been recorded; in fact, only one reference has been found—that of Sir Russell Brain (1947), who, writing on the treatment of migraine, states: "Ergotamine tartrate has a highly specific effect on the headache . . . there seems no risk of ergotism, but pregnancy and arteriosclerosis are contraindications, and, rarely, a single dose may cause thrombophlebitis."

Below are given the case histories of three patients who in one practice in the course of two years have developed bilateral thrombophlebitis following a single dose of ergotamine tartrate.

Case 1

A married woman aged 42, with two children, was diagnosed by an ophthalmic surgeon in 1954 as suffering from migraine, precipitated by strong sunlight. The wearing of dark glasses seemed to prevent the recurrence of any severe attacks, but ergotamine tartrate ("femergin") was prescribed in case of need.

On May 11, 1955, she developed an acute attack of migraine and took her first dose of ergotamine (two 1-mg. tablets) at 11 a.m. About 2 p.m. the headache disappeared quite suddenly, but she experienced a cramp-like pain in her right calf. This pain persisted and grew in severity throughout the afternoon and evening. In the night she was very restless with the pain and began to have sharp pains in the left leg. In the early hours of the following morning she was unable to stand up.

Examination later that morning showed that she was afebrile and had no gross varicose veins; but a dull red line, which was very tender, was present over the course of the long saphenous veins in the right leg, extending about a quarter of the way up the right thigh. A similar red line, also very tender, was present in the left leg, but this did not extend above the knee.

Both legs were strapped with "elastoplast," sorbo-rubber strips covering the affected veins, and she was encouraged to be ambulant. Within 24 hours she was much easier, all symptoms had gone within four days, and when the strapping was removed after 12 days there was no evidence of any residual thrombosis. She did show some varicosity of the long saphenous veins, more marked in the right leg.

Case 2

The patient, a married man aged 44, had a history of marked varicose veins in both legs, for which he had had injections in 1942, which had been followed by a troublesome phlebitis. This had dissuaded him from any surgical procedure, and he had resigned himself to a below-knee elastic support. He had also managed to change from a manual occupation to a sedentary job in May, 1956—a change which had relieved his leg symptoms but aggravated his migraine.

On July 19, 1956, he received his first prescription for ergotamine tartrate, and on July 23 he had a typical migraine attack on rising. He took two 1-mg. tablets sublingually about 9 a.m. (it was Sunday) and then had a little breakfast. His headache began to ease and he decided to seek some fresh air in the garden. About 10.30 a.m. he was compelled to return indoors with severe pains in both legs. The pains increased, and by lunch-time he was only capable of lying on his bed. After a restless day and night he found numerous red lines on both legs.

Examination then revealed an intensive network of very tender red lines over both legs and extending half-way up each thigh. He was admitted to hospital, and the following day both long saphenous veins were ligated at the saphenous opening to obviate the danger of pulmonary emboli. He made a steady recovery.

Case 3

A married man, a shop-proprietor aged 44, whose mother had suffered from asthma, was first diagnosed as suffering from migraine in 1952. Codeine tablets usually relieved the attacks, but in February, 1957, they became more frequent and he was subsequently kept on a modified Gowers mixture as a preventive. On March 23 he had his first prescription for ergotamine in the form of "cafergot."

On April 5 he felt a typical attack starting on rising. He returned to bed and swallowed his first dose of ergotamine tartrate (two tablets) at 10.30 a.m. He fell asleep, and awoke at 2 p.m. with his headache gone but having severe pains in the varicose veins in both calves. He remained in bed, and slept through the early part of the night, but found himself unable to stand the next morning owing to severe pains in both legs, the left being the worse.

Examination revealed a tender red line over a vein in his left leg, extending for about 4 in. (10 cm.). He had a small area of tenderness over a vein in the right calf but no redness. Both legs were strapped with elastoplast; he was much better in 48 hours, and when the strapping was removed after one week no signs of thrombosis or phlebitis were present.