Nevertheless, it is universally acknowledged now that the most likely hypothesis is that a neurotropic virus is responsible for the production of these conditions.

Pathology

There are acute inflammatory lesions, with demyelination and perivascular infiltration. The destroyed myelin substance is absorbed by the microglial phagocytes. The axis cylinders degenerate and proliferative gliosis is the final sequence. The neuritis is characteristically retrobulbar, since the nerve fibres which are myelinated are attacked. The myelitis in some 50 per cent of cases proves fatal due to the ascending involvement of vital centres in the medulla. In neuromyelitis optica as in acute encephalomyelitis, the incidence of bilateral and extensive involvement is greater and remission is a rarity.

Thus Devic's disease is an acute infection, without any demonstrable definite causative factor. The symptoms presented are those of ascending myelitis and bilateral optic neuritis which are simultaneous. Other characteristics are that there is no specific age group, the course of the disease is rapid and more often than not is fatal. The laboratory, serological and urinalysis findings are negative.

Since thiamin chloride remains in the cerebrospinal fluid for a longer time when injected into and mixed thoroughly with the C.S.F. and since it is excreted very slowly, if given by this route, it is rational to believe that it would exert a definitely beneficial effect on the central nervous system. Again since experimental avitaminosis B_1 reveals marked myelin degeneration in the spinal cord as well as in the peripheral nerves (Gildea *et al.*, 1936), it is logical to believe that intrathecal vitamin B_1 therapy should be the one of choice. Stern (1938) reports very favourable results in his 2 cases of multiple sclerosis treated by the intrathecal route. The patient described and treated by me received 10 intrathecal injections between 2nd March, 1948, and 15th July, 1948. The maximum dose given was 60 mg. According to Stern (1938), 100 mg. of vitamin B_1 injected intrathecally might prove fatal. So it is dangerous to exceed this dose, or even to approach very near this limit.

Now of course to be honest, whether it is the vitamin B_1 given intrathecally or whether it is the normal course* of the disease, that has given such spectacular results, who can tell? Coincidence of treatment with natural improvement* is a very misguiding and disconcerting factor in the assessment of the therapeutic value of different remedies.

*Remission is not a feature of this disease according to Wachsler, W. E., 1947. A Textbook of Clinical Neurology, W. B. Saunders Co.—EDITOR, *I.M.G.*

Summary

A rare case of a rare disease neuromyelitis optica is reported, wherein the patient was affected with the disease, and received continuous treatment for one year without any benefit. Thereafter, 10 injections of vitamin B_1 in increasing doses and at certain intervals were given intrathecally to the patient who responded well to this treatment apparently, and ultimately recovered her vision to some extent as well as recovered from the paraplegia. The sudden death, full 3 months after the last dose, is inexplicable since the patient was not seen after the death, nor was post-mortem examination possible. The perimetric examination of the patient's field of vision was not possible due to her age.

REFERENCES

ALLBUTT, C. (1870) .. *Lancet, i,* 76.
BERLINER, M. L. (1935). *Arch. Ophthalmol.,* **13,** 83.
DEVIC (1894) .. *Congress Medical International.* Lyons.
ERB (1879) .. .. *Arch. Psychol.,* **10,** 146.
GILDEA, M., CASTLE, W. B., GILDEA, E. F., and COBB, S. (1936). *J. Nerve and Mental Dis.,* **83,** 505.
PATON, L. (1936) .. *Arch. Ophthalmol.,* **15,** 1.
STERN, E. L. (1938) .. *Amer. J. Surg.,* **39,** 495.

THE TREATMENT OF FEMALE GENITAL DISORDERS WITH STEROID HORMONES

By W. KIRLOSKAR, M.D. (Kiel), Germany

A report on 700 cases

IT is my object in the present article to give an account of a few of the various female genital disorders and the treatment adopted by me with hormones during the last 12 years.

(A) Treatment with female hormones

The rationale of oestrogen therapy is based upon certain physiological considerations. The female hormones produced by the ovaries are oestrin and progesterone. While the former is secreted continuously from almost the very beginning of life, in the mature female its effects are responsible for the maintenance of such secondary sex characteristics as the shape of the female breasts, the size of the adult uterus and adnexa, and the 'oestrus' condition of the vaginal mucosa. Progesterone, on the other hand, is secreted in the menstrual cycle only for a few days every month.

The physiological actions of the two hormones are entirely different. Oestrin is essential for the development of the sex organs and determines feminity, and its absence will prevent ovulation and consequently there will be no menstruation. It sensitizes the uterus and increases its vascularity and motility while progesterone desensitizes

it and inhibits its motility thus allowing the nidation of the ovum and preventing the occurrence of abortion. Both hormones are necessary for menstruation and pregnancy to occur.

Deficiency of those hormones brings about the various disorders which have to be treated by supplying the body with an adequate amount of them to make good the shortage and thus correct the various abnormalities that occur as a result.

Endocrine therapy in the human female has undergone considerable changes in the past few years and of practical value in the management of clinical endocrine problems in women are the two synthetic female hormones oestradiol and progesterone. These preparations have been used during my practice abroad and in this country for twelve years, and the results obtained in their varied applications are given below. The treatment was carried out in the following main disturbances :

(1) Hypogonadism, hypoplasia and infantilism.

(2) Primary amenorrhœa.

(3) Hypomenorrhœa.

(4) Disturbances and deficiencies during the climacteric.

(5) Eczema.

(6) Metropathia hæmorrhagica.

(7) Habitual abortion.

(8) Threatened abortion.

Case reports

(1) *Hypogonadism, hypoplasia and infantilism* (combined with dysmenorrhœa and sterility).—Average age of the patients 18 to 20 years; married, coitus painful. The internal examination showed a small uterus, not completely developed and the examination was painful.

Average periodical cycle 5 to 7 weeks, scanty flow oligomenorrhœa.

Treatment.—Five injections of oestradiol dipropionate, 1 mg. each, were given with an interval of 3 to 4 days, starting with the cessation of the last period. The course of the treatment was 2 to 3 months. Most of the patients had their regular periods after the 2nd course but to be on the safe side a 3rd course was also given. The final examination after the full course of treatment revealed a normal development of the uterus; no pains during examination of coitus were felt. The vaginal secretion was present and in several cases conception was seen after the treatment.

Number of cases treated : 308.

(2) *Primary amenorrhœa.*—The age of the patients was 16 years and over. Some of them were virgins, though married, on account of fear of pain during tried cohabitation. They were brought by their husbands. In most cases the patients were infantile, frightened and eagerly awaiting the result of the examination, which in nearly all cases showed a small undeveloped uterus, about the size of a big walnut, mostly retroverted, hard and dried up. There was no libido. The vagina was dry, the hair on the mons veneris scarce, the breasts were small and undeveloped and the hips of a masculine type. These patients never menstruated.

Treatment.—Four injections of 5 mg. each of oestradiol dipropionate were given intramuscularly into the buttocks with intervals of 5 days (in some cases in combination with anterior pituitary hormone, daily 1 cc.). Six days after the last injection of oestradiol dipropionate the treatment was continued by 3 injections of progesterone, 5 mg., every second day to complete the cycle. The same course of treatment with oestradiol dipropionate and progesterone was repeated during 2 or 3 cycles. Within this period the uterus and pubic hair developed normally; the breasts and buttocks showed a more feminine shape; nervousness and fear of cohabitation disappeared in about 95 per cent of the cases. The patients became more self-confident. A normal menstruation was experienced for the first time, and continued regularly every month.

Number of cases treated : 150.

(3) *Hypomenorrhœa (primary).*—In all these cases a regular but scanty flow of menstruation was observed.

Treatment.—After the cessation of the last menstruation the following treatment was given :

First day 1 mg. oestradiol dipropionate intramuscularly; 2nd, 3rd and 4th days 1 mg. oestradiol orally per day; on the 5th day 1 mg. oestradiol dipropionate intramuscularly; on the 6th, 7th and 8th days 1 mg. oestradiol per os and so on until the 21st day ending with an injection. Three days before the expected period, one tablet of anhydrohydroxyprogesterone 5 mg. was given and this dosage was continued during the first two days of the menses. The menses became normal after 3 to 4 cycles of the above treatment. To be on the safe side this was continued for 3 months by oral administration of 15 oestradiol tablets of 1 mg. during the first 15 days of the intermenstruum and 5 tablets of anhydrohydroxyprogesterone during the last 3 days of the intermenstruum and the first 2 days of the menses (and so on). All cases of hypomenorrhœa were treated successfully.

Number of cases treated : 79.

(4) *Disturbances and deficiencies during the climacteric,* such as senile vaginitis, pruritus and kraurosis vulvæ, loss of pubic hair, arthroses, psychic depressions, flushings, etc.

Treatment.—One mg. of oestradiol dipropionate intramuscularly every 3rd to 4th day and local applications of oestradiol ointment were given until the symptoms vanished. 93 per cent of these cases were treated successfully.

Number of cases treated : 30.

(5) *Eczema.*—For the treatment of feminine eczema during the menopause oestradiol ointment was used with great success. Successfully treated : 83 per cent of the cases.

Number of cases treated : 36.

(6) *Metropathia hæmorrhagica.*—Ten mg of progesterone were given intramuscularly every day until the bleeding stopped. Duration of this treatment : 10 to 20 days. After an interval of a week to a fortnight the injections were repeated a few days before the expected menstruation. This treatment was discontinued only when the period was normal. After the menses had become normal a supplementary course of 1 tablet of 5 mg. anhydrohydroxyprogesterone per day was given (5 days before the commencement of each menstruation) and was continued for 6 months. The results were satisfactory in all cases.

Number of cases treated : 12.

(7) *Habitual abortion.*—In cases of habitual abortions, as soon as pregnancy was diagnosed, the following treatment was given :

Five mg. of progesterone were injected intramuscularly every second day. Then the dosage was gradually reduced to 2 mg. every 3rd or 4th day. During the days corresponding with the past menstruations 5 mg. a day were given by injection. From the beginning to the end of the pregnancy 1 tablet of 50 mg. vitamin E per day was given. This treatment proved successful in 80 per cent of the cases.

Number of cases treated : 15.

(8) *Threatened abortion.*—Some of the pregnant women came after the first signs of bleeding, some, however, only after 2 or 3 days of bleeding. In all cases 10 mg. of progesterone were given intramuscularly every day until the symptoms ceased. The dosage was then reduced slowly to 5 mg. and the interval increased to 2, 3 and 4 days. Finally, the treatment was continued by the oral administration of 5 mg. of anhydrohydroxyprogesterone per day. Vitamin E was given in all these cases for at least 3 months. The administration of anhydrohydroxyprogesterone was discontinued 6 weeks after the first signs of threatened abortion. The usual methods of treating threatened abortions were applied, *i.e.* rest in bed with the foot-end of the bed raised as against the head-end. In 3 cases the bleeding re-occurred. In these cases the treatment was repeated with 10 mg. of progesterone intramuscularly until the cessation of bleeding. 77 per cent of the cases were treated successfully.

Number of cases treated : 25.

(*B*) *Treatment with male hormones*

In the treatment of premenstrual pain in the mammæ, testosterone propionate was given with great success. In most cases one injection of 10 mg. intramuscularly was fully successful. In cases, however, where the pain was not relieved by this treatment, 3 injections of 10 mg. of testosterone propionate on successive days were given. The treatment was successful in 100 per cent of the cases.

Number of cases treated during the last 16 months : 45.

Table

Indications	Number of cases	Treatment	Number of cases treated successfully	Percentage of successfully treated cases
Hypogonadism, hypoplasia and infantilism.	308	Oestradiol dipropionate	308	100
Primary amenorrhœa ..	150	Oestradiol dipropionate and progesterone, in a few cases in combination with the anterior pituitary hormone.	142	95
Hypomenorrhœa	79	Oestradiol dipropionate, oestradiol and anhydrohydroxyprogesterone tablets.	79	100
Disturbances and deficiencies during the climacteric.	30	Oestradiol dipropionate and oestradiol ointment.	28	93
Eczema	36	Oestradiol ointment	30	83
Metropathia hæmorrhagica ..	12	Progesterone and anhydrohydroxyprogesterone tablets.	12	100
Habitual abortion ..	15	Progesterone. Vitamin E was administered additionally.	12	80
Threatened abortion ..	25	Progesterone and anhydrohydroxyprogesterone tablets. Vitamin E was administered additionally.	19	76
Premenstrual pains in the mammæ.	45	Testosterone propionate	45	100
Total number of cases ..	700		675	96.4

Summary

During the last 12 years notes were made on 700 cases of female genital disorders, such as hypogonadism, hypoplasia, infantilism, primary amenorrhœa, hypomenorrhœa, disturbances and deficiencies during the climacteric, eczema, metropathia hæmorrhagica, habitual abortion and threatened abortion. In 675 of these cases, *i.e.* 96.4 per cent were treated successfully with oestradiol dipropionate, oestradiol progesterone, anhydrohydroxyprogesterone or a combination of the above-mentioned ovarian and corpus luteum hormones, and some cases with testosterone propionate. In habitual abortion vitamin E was administered in addition to treatment with progesterone. In threatened abortion the treatment with progesterone and anhydrohydroxyprogesterone was also combined with vitamin E per os. In primary amenorrhœa, the anterior pituitary hormone was given in some cases in addition to the above oestrogenic and luteal hormones.

The results of the treatment with steroid hormones given in the table and showing a success in 96.4 per cent of the cases are very encouraging indeed. No adverse by-effects on account of the above treatment were ever seen during all these 12 years.

The preparations used in the above study were : oestradiol dipropionate 'Ciba' (ovocyclin P); oestradiol 'Ciba' (ovocyclin); progesterone 'Ciba' (lutocyclin ampoules); anhydrohydroxyprogesterone 'Ciba' (lutocyclin tablets); and testosterone propionate 'Ciba' (perandren).

PROGESTERONE IN THE TREATMENT OF MALARIA

By S. J. GROSS, M.D.

Bombay

I SUGGESTED in a previous communication (Gross, 1947) that sex hormones participate in the mechanism of malaria. Abortions, sterility, impotence, menstrual disorders, greater susceptibility of women to malaria, predominance of female parasites in the blood, and recurrences of malaria at regular intervals of 3 to 4 weeks are manifestations and sequelæ of malaria which strongly suggest the participation of female hormones in the pathogenesis of malaria.

My original observations were made on men. In the meantime I have observed a number of malarial attacks in women. It is interesting that most of the women had the first attack of fever generally 2 to 3 days before menstruation or the expected date of their periods. I have observed this onset of malarial fever, first attacks and not relapses, shortly before menstruation so often and so regularly that I am inclined to regard fever 2 to 3 days before menstruation as a diagnostic sign for malaria.

Shortly before menstruation the secretion of progesterone decreases and the secretion of oestrogen begins, both hormones being at a low level with follicular hormone in the ascendancy. A similar, though reversed, condition is encountered shortly before ovulation when the secretion of oestrogen decreases and the secretion of corpus luteum hormone increases. Putnam, Boyd and Mead (1947) reported periodic or cyclically recurring phenomena of vivax malaria in which a 12 to 13 days' rhythm or recrudescence is described. The authors have no explanation to account for it, except unknown aspects of the schizogonous cycle of the parasite. I believe that these cyclical recurrences can be explained by the normally occurring rhythmical changes in the hormonal level which enhance the onset of malarial attacks and of malarial relapses.

The known antimalarial drugs are excellent for the treatment of the acute malarial attack. However, they do not eradicate the infection and do not prevent the onset of relapses. Monk (1948) in a review of modern therapy of benign tertian malaria tabulates the results of 28 investigations with different drugs and different methods. From this table the average of the relapse rates is found to be 33.87 per cent. This indicates clearly that parasiticidal therapy alone is not sufficient. I have obtained and reported good results in the prevention of relapses with the administration of male hormones. It has been objected that male hormones might cause virilism when given to women patients (Deshmukh, 1947). This objection cannot be entertained, because in these cases testosterone propionate is given against an alleged excess of female hormones, and the dosage used and suggested is too small to cause any virilism. However, when given in the acute stage of the attack, these hormonal injections caused not too infrequently a rise of temperature. This rise does not occur when the injections are given in the convalescent stage.

Therefore I was looking for some hormonal preparation which could be given in the acute stage without causing any rise of fever. Corpus luteum hormone is the natural and logical choice. Follicular hormone is counteracted not only by the male hormones but to a certain extent also by progesterone. Corpus luteum hormone resembles the male hormone in some of its effects. This bi-sexual character of progesterone may be related to the fact that chemically it resembles much more the male than the female hormone. Progesterone is found in the adrenal cortex and it has been shown conclusively that the lives of adrenalectomized rats, ferrets and dogs will be prolonged by progesterone (Anderson and Bolin, 1940). In this connection it may be recalled that 'the implication of the adrenal gland is held to be responsible for algid malaria symptoms observed