PROGESTERONE IN THE TREATMENT OF MIGRAINE

INDER SINGH
M.B. Rangoon, M.R.C.P.E., F.R.F.P.S.
LIEUT.-COLONEL I.M.S.

INDERJIT SINGH
M.B. Rangoon, Ph.D. Camb., M.R.C.S., F.A.Sc.
CAPTAIN I.M.S.

DEVINDER SINGH
L.S.M.F. Punjab

THE ætiology of migraine is complex and varied. Individual susceptibility, often inherited as a mendelian dominant, seems to play an important part, and in any given person more than one factor may precipitate an attack, though there is usually a particular predisposing factor.

In some cases endocrine abnormality may be responsible. It appears that thyrotoxicosis predisposes to migraine, patients with exophthalmic goitre being specially liable; but this may be due to the effect of increased pulse-pressure in thyrotoxicosis in a migrainous subject. The onset of migraine at or shortly after puberty and its disappearance with old age suggest that imbalance of sex hormones may be an ætiological factor. In this connexion it is interesting to note its association with the menstrual cycle (menstrual migraine) and its disappearance with the menopause. Therapeutically, 'Emmenin' (Blakie and Hossack 1932) and anterior pituitary-like hormone (A.P.L.) (Moffat 1937) are said to have given beneficial results.

We record here our results in 23 cases of migraine in women, in whom, clinically and therapeutically, œstrogens were established as causal factors in precipitating attacks of migraine. The patients were all successfully treated with progesterone, which not only terminated but also prevented attacks. Facilities for biochemical examinations were not available.

SYMPTOMS

The patients were women between the ages of 21 and 40, and in all of them migraine was the predominant symptom. Its duration varied from about three years in the younger patients to about fifteen years in the oldest. The relation of migraine to menstruation was as follows:

About mid-cycle	12
Premenstrual	4
About mid-cycle and premenstrual	7

The incidence of associated symptoms was as follows:

Excessive and/or prolonged menstruation	16
Intermenstrual bleeding	5
Loss of appetite, lassitude, poor concentration, improper sleep, and vague headaches	21
Indigestion, unclassified	1
Hyperchlorhydria	1
Falling of hair	2
Pain in calf muscles and burning sensation in soles	1
Patchy pigmentation of thighs	1
Tendency to obesity	1
Pallor	3

They were otherwise all healthy, except for the following physical signs in a few cases:

Anæmia	7
Salpingitis	2
Retroverted uterus	4

These 23 cases in which there was clinical evidence of œstrogen hyperactivity form part of a group of 30 cases of migraine in females, which had responded inadequately to the usual methods of treatment. In 27 other cases such treatment had given satisfactory results.

Œstrogen hyperactivity commonly manifested itself in disturbances of menstruation, such as excessive and/or prolonged periods. When these were not present, sensitiveness to œstrogens was shown by inducing a migrainous attack with œstradiol. In all 23 cases migraine could be induced or increased by oral or parenteral administration of 2–10 mg. of œstradiol ('Clinœstrol'), and was relieved by the administration of 5–15 mg. of progesterone ('Lutocyclin'). Usually the amount of progesterone required to alleviate an induced attack of migraine was inversely proportional to the amount of œstradiol used to induce it. To prevent spontaneous attacks the amount of progesterone required was generally directly proportional to the severity of the symptoms of œstrogen hyperactivity.

In no case did we inform the patient of the nature and action of the drugs used, and the relief from migraine was associated with disappearance of symptoms of œstrogen hyperactivity. Accordingly, it is unlikely that the success of treatment was due to suggestion. The effects of the drugs were uniform, œstradiol aggravating the symptoms and progesterone relieving them. Early in our trials we treated 7 control cases by injections of distilled water without any effect on the migraine.

ILLUSTRATIVE CASE-RECORDS

Case 1.—Female, aged 40. Periods began at 13. Married when 19. Last and only pregnancy seventeen years ago. Migraine started two years after this pregnancy. Onset at any day between the 10th and the 16th days of the cycle, usually between the 11th and the 13th, rarely premenstrual between the 24th and the 28th days. Periods somewhat excessive and prolonged. Premonitory symptoms of migraine included irritability and a tendency to weep, mutism, and seclusion in bed, loss of memory for time and place, and inability to continue conversation, followed by dimness of vision, blindness, visual hallucinations of snakes and tigers, tingling sensation in, and paresis of, the left upper limb, swelling of the hand and tongue (which continued during the attack), and vomiting. Analgesics, bromides, phenobarbitone, and ergotamine tartrate had an unsatisfactory effect. Complete relief was obtained with two doses of lutocyclin, 2 mg. on alternate days. Period of freedom after treatment with this dosage lasted eight weeks. Relapse occurred about mid-cycle and was controlled with 5 mg. of lutocyclin. Attacks are now mild and less frequent, always occur about mid-cycle, and are easily controlled and prevented by lutocyclin.

Case 2.—Female, aged 29. Periods began at 12. Married when 21. Last and only pregnancy seven years ago. Migraine started two years after this pregnancy. Onset any day between the 4th and the 28th days of the cycle. Periods scanty, lasting 2–3 days. Comparative freedom from migraine during this time, though sometimes the most severe attacks developed two days before to three days after the period.

Three months after the onset of migraine scanty intermenstrual bleeding became very frequent, sometimes lasting several days. Continuous ordinary headache or migraine attacks were often associated with intermenstrual bleeding, and their severity was to some extent proportional to the amount of bleeding.

Premonitory symptoms were severe, with giddiness, cold sweating, cloudiness of vision, and diplopia. Analgesics, bromides, phenobarbitone, and ergotamine had little effect except that the last was useful during the actual attack. Complete relief was obtained with four doses of lutocyclin 2 mg. on alternate days. Intermenstrual bleeding stopped. The following period was scanty and lasted two days. The migraine recurred on the 6th day of menstrual cycle, but complete relief was obtained with 5 mg. of lutocyclin. Period of freedom then lasted six weeks. Attacks are now mild and less frequent, usually occurring about mid-cycle; they are easily controlled or prevented by lutocyclin in smaller dosage.

Case 3.—Female, aged 29. Periods began at 13. Married when 18. Migraine started at 13 with onset of menstruation. The attacks were severe and associated with excessive menstruation. They were usually mid- and pre-menstrual but at times bore no relation to the period. There was progressive falling of hair.

She aborted three times in early pregnancy during the first six years of married life. The fourth pregnancy, five years ago, appears to have been maintained by administration of crude whole-placenta extracts by mouth. Three months after the onset of this pregnancy migraine disappeared, to return six months after parturition. Now, however, the attacks were mild and irregular; the periods were less excessive, and the loss of hair within normal limits. In the fifth pregnancy, twenty months ago, migraine ceased after three months and did not recur till five months after parturition. The attacks were mild and irregular, often premenstrual, and associated with excessive periods and

premenstrual eruptions of acne. The acne was very pronounced when the following period was more excessive than the previous one. All symptoms subsided with lutocyclin, and this is now a very good preventive in gradually diminishing dosage.

Case 4.—Female, aged 36. Periods began at 14. Married when 17. There were six pregnancies during the first nine years of married life, the last being ten years ago. Migraine, lasting seven years, started about three years after this pregnancy. The attacks were severe and frequent, without any definite relation to the menstrual periods, which were normal. Treatment for a retroverted uterus and right-sided salpingitis, and for indigestion, did not affect the migraine; nor did vitamin B_1 given in large doses for pain in the calf muscles (at times very severe), and burning of the soles, of three years' duration. Wassermann reaction and Kahn tests were negative.

She became pregnant again sixteen months ago, and migraine ceased after the fourth month of pregnancy but recurred six months after parturition. The symptoms referred to the legs and stomach also ceased during pregnancy, and reappeared with migraine after parturition. All symptoms have responded to lutocyclin.

RELATION OF SYMPTOMS TO VARIATIONS IN EXCRETION OF ŒSTROGENS AND PROGESTERONE

In these cases a definite relation exists between the attacks of migraine and the time at which the excretion of free œstrogen in the urine would be expected. Thus mid- and pre-menstrual attacks of migraine correspond to the periods when free œstrogen is excreted in the urine. Its disappearance with the progress of pregnancy corresponds to the increased ratio of œstriol to œstrone in the urine, the absence of œstradiol in the blood, and the increased excretion of progesterone in the urine.

Clinically, progesterone both cured and prevented migrainous attacks, whereas stilbœstrol precipitated an attack identical with the naturally occurring one. The excretion of A.P.L. also rises during pregnancy, and A.P.L., by stimulating the development of corpora lutea, is largely responsible for the increased production of progesterone. Individual susceptibility or intolerance to œstradiol was probably an important factor in the causation of migraine in these cases.

Experimentally, headache which may simulate a migrainous attack, severe nausea and vomiting, aches and pains all over the body, especially in the calf muscles, and intense pallor occur singly or in combination in a few persons who are susceptible to stilbœstrol therapy. Milder symptoms are lassitude and languor, loss of appetite, lack of concentration, and vague headaches. Such mild symptoms were complained of by nearly all our migraine patients. Response to treatment with progesterone was complete.

An interesting feature in case 4 was the disappearance of indigestion and pains in the legs, along with migraine, after the fourth month of pregnancy and for six months after parturition. In an almost identical case, where by test-meal examinations it was found that indigestion resulted from hyperchlorhydria and hypersecretion, a fall in the gastric acidity, accompanied by spontaneous disappearance of gastric symptoms and migraine as pregnancy progressed, was noticed. A similar but smaller fall was noticed with progesterone therapy, which relieved the migraine. This and scanty evidence available from a few other cases suggest that progesterone depresses the gastric secretion, probably via the pituitary-hypothalamic mechanism, though retention of sodium in the body caused by progesterone may have an adjuvant effect. Way (1945) has produced evidence that the gastric acidity and the urinary excretion of A.P.L. in pregnancy in women seem to be inversely proportional. It appears from experiments on dogs by Culmer et al. (1939) that A.P.L. diminishes the secretion of free and total acid, and progesterone does not have this effect. These findings suggest the following explanation of our observation in this case: pregnancy→increased A.P.L. (and therefore hypochlorhydria)→increased progesterone→relief of migraine.

The menstrual disturbances present in some cases suggested hyperactivity of the œstrogens and also responded to progesterone therapy. In one case patchy progressive pigmentation of the skin had developed after three years of migraine; this also has been checked with progesterone therapy, and is gradually subsiding.

MODE OF ACTION OF ŒSTROGENS

Headache or migraine may be caused by œstrogens in one or more of the following ways:

(1) *By causing temporary enlargement of the pituitary.*—Œstrogens injected into rats of both sexes cause pituitary enlargement (McEuen et al. 1936, Zondek 1936). In the migraine subjects, however, such gross changes are not evident in X-ray films. It is reasonable to assume that even congestion of the pituitary produced by œstrogens would precipitate headache or migraine in them.

(2) *By their effect on blood-vessels.*—The specific effect of ergotamine tartrate on the headache, by virtue of its vasoconstrictor action, is well known. Dilatation of the blood-vessels in the distribution of the common carotid artery, as shown by flushing of the face, conjunctiva, and nasal mucosa of the affected side, leads to vigorous pulsation of the arteries and increased stimulation of the sensory nerve-endings in their coats, and this is probably the cause of headache in migraine. Early cortical symptoms have been attributed to arterial spasm preceding vasodilatation. According to this hypothesis migraine is caused by arterial spasm followed by arterial dilatation within the distribution of the common carotid artery.

Nothing seems to be known about the effect of œstradiol on cerebral blood-vessels, except that intense congestion and hæmorrhages may occur in the pituitary. The results of Markee's (1940) experiments are, however, interesting.

Using a macaque monkey he transplanted a uterine graft to its eye. In the first half of the menstrual period, under œstrogenic stimulation, this graft showed alternate vasodilatation and vasoconstriction of certain areas. At the time of ovulation the vasodilatation was well marked. Just before menstruation vasoconstriction occurred for a day or so and the graft was blanched. This was followed by vasodilatation and rupture of small arteries. It is not known whether the vascular changes in the graft were local and confined to it, or secondary to similar changes in the blood-vessels of the eye. But, if comparison may be made, the primary vasoconstriction followed by vasodilatation in this case is identical with the conception that migraine is due to arterial spasm followed by arterial dilatation within the distribution of the common carotid artery.

(3) *By retention of sodium and chlorides in the body.*—Thorn et al. (1940) have shown that œstradiol injected into normal dogs causes retention of sodium and chlorides. Retention of sodium and chlorides in the brain tissues would predispose to cerebral œdema of the affected areas, and cerebral œdema would certainly lead to headache. However, this would not explain the beneficial effect of progesterone, since progesterone is also known to cause retention of sodium and chlorides. It is reasonable to assume, however, that in therapeutic doses, progesterone would convert œstradiol into the comparatively impotent œstrone and œstriol, and so be utilised instead of circulating in the blood as free progesterone. Very large doses of progesterone also cause headache, and in this connexion it may be mentioned that Hamblen (1939) reported a case of menstrual headache associated with excretion of abnormally large amounts of sodium pregnandiol glycuronide, and relieved it with intensive œstrogenic therapy.

SUMMARY

Of 30 women with migraine which had responded poorly to the usual methods of treatment, 23 showed

signs of excessive œstrogen activity. In all of these it was shown that œstrogens would precipitate an attack. In all 23 cases progesterone was effective in relieving or preventing attacks of migraine. Various associated symptoms also disappeared with its use.

The name "œstrogenic migraine" might be appropriate for this condition. These symptoms also responded to progesterone. This clinical variety of migraine may be termed œstrogenic migraine.

In a case with a tendency to obesity progesterone had no effect on the obesity, though the migraine was successfully treated.

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CEREBRAL ANGIOMATA IN AN ICELANDIC FAMILY

H. A. KIDD
F.R.C.S.E.
SURGEON,
ST. HELIER HOSPITAL,
CARSHALTON

J. N. CUMINGS
M.D. Lond., M.R.C.P.
CLINICAL PATHOLOGIST,
NATIONAL HOSPITAL, QUEEN SQUARE, LONDON

Elkington [1] in 1935 described some cases with symptoms suggesting that an angiomatous condition in the brain was their pathological basis, and this was confirmed in one case by autopsy and histological findings.

We have clinical, autopsy, and histological records of a patient from Iceland who showed such an angioma in the cerebral white matter, and clinical and autopsy records in a cousin, together with a remarkable family history in which sudden death in young persons is a prominent feature.

The clinical details of the two patients seen by one of us (H. A. K.) are as follows:

Case 1.—A man, aged 22, was admitted to hospital on April 13, 1938, in coma. There had been one previous attack of unconsciousness eight months previously. On admission there was twitching of the face, arm, and leg on the right side, with spasticity of the limbs, more pronounced on the left side. The pupils were equal and reacted to light. No other significant clinical findings were present, and the blood-pressure was normal. Lumbar puncture yielded a bloodstained fluid under an initial pressure of 125 mm. The cerebrospinal fluid (C.S.F.) showed 43 lymphocytes per c.mm., 0·5 g. of protein per 100 c.cm., a positive Pandy, and a negative Wassermann.

Two days later the patient was confused and aphasic, but able to move the limbs, and had extensor plantar responses.

1. Elkington, J. St. C. *Lancet*, 1935, i, 6.

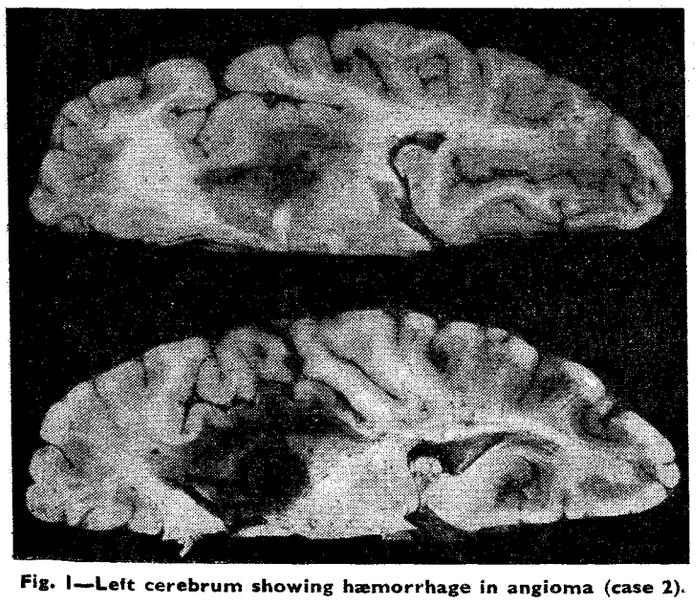

Fig. 1—Left cerebrum showing hæmorrhage in angioma (case 2).

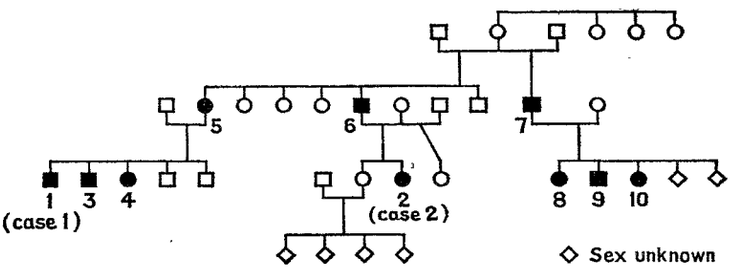

Fig. 2—Pedigree showing relations of cases 1 and 2: solid symbols indicate cerebrovascular accidents in youth; open symbols indicate absence of cerebrovascular accidents in youth.

There was papilloedema of the right disk. The C.S.F. was still bloodstained, with an initial pressure of 165 mm. After six days the left pupil was dilated and the right contracted, but other signs were similar to those seen previously. Stupor increased, and he died twelve days after admission to hospital.

Autopsy.—There was a cyst containing yellow fluid in the left temporal lobe and a large recent hæmorrhage in the right temporoparietal lobe. No aneurysm or vascular disorder was seen. The hæmorrhage was so extensive that it was impossible to demonstrate any angioma.

Case 2.—A woman, aged 33, cousin of case 1, was first admitted to hospital on Jan. 15, 1940, with a history of numbness on the left side for three weeks. There was slight loss of power of the left arm and leg, with exaggerated reflexes on that side, and flexor plantar responses. A slight nystagmus to the left was present. No other abnormal physical signs were found, and blood-pressure, blood-count, and C.S.F. were normal. There had been a similar but milder attack eighteen months previously.

She was discharged with a provisional diagnosis of intracerebral hæmorrhage and was to return for ventriculography if symptoms persisted. She was readmitted on Nov. 5, 1942, with a week's history of aphasia and weakness of the extremities. A left hemiparesis and some degree of aphasia were present. Coma ensued, and she died four days later, but further clinical notes are not available.

Autopsy.—Abnormal features were limited to the head; the cardiovascular system was normal. The brain was fixed whole and on section showed a hæmorrhage in the white matter of the left hemisphere. This was situated to the lateral aspect of the lateral ventricle, externally and posteriorly to the basal ganglia, extending almost to the posterior tip of the posterior horn, and almost to the cortical grey matter (fig. 1).

Sections cut in celloidin showed a large hæmorrhage with very dilated vascular channels, some of which showed well-marked elastica. The surrounding brain tissue showed much iron pigment, some cuffing of the vessels by lymphocytes, and a few small vessels plugged by thrombus. Some of the many peripheral capillaries were irregular in shape and arrangement, and the appearances were those of an angiomatous condition in which hæmorrhage had taken place.

FAMILY HISTORY

Dr. Arni Pjetursson, of Reykjavik, has kindly supplied the following remarkable details of the family history (fig. 2):

1. Pjetur (case 1) .. died aged 22.
2. Inga (case 2) .. ,, ,, 35.
3. Jakob .. .. ,, ,, 23, brother of 1.
4. Gudrun .. .. ,, ,, 23, sister of 1.
5. Kristjana .. ,, ,, 36, mother of 1.
6. Ingimar .. .. ,, ,, 30, father of 2, brother of 5, drowned in a swimming-pool although a good swimmer.
7. Hans .. .. ,, ,, 42, half-brother of 5 and 6.
8. Elinborg .. .. ,, ,, 25, daughter of 7.
9. — .. .. ,, ,, 27, brother of 8.
10. — .. .. ,, ,, 29, sister of 8.