THE SEROTONIN ANTAGONIST 1-METHYL-D-LYSERGIC ACID BUTANOLAMIDE (UML-491) OR METHYSERGIDE ('DESERIL')

ITS PHARMACODYNAMICS AND EFFECTS ON 'MIGRAINE TYPE' VASCULAR HEADACHES

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'MIGRAINE TYPE' VASCULAR HEADACHES

In 1937, Graham and Wolff[1] demonstrated that ergotamine produced constriction of the cranial blood vessels, thereby giving symptomatic relief from certain vascular headaches.

Wolff *et al.*,[2] during 1953, proved that attacks of 'migraine' are accompanied by perivascular inflammation of cranial vessels and that an exudate occurs in the vascular coats of the vessels concerned. Concurrently, there is lowering of the pain threshold, alteration of capillary permeability and increasing susceptibility to vascular injury.

In 1957, Ostfeld *et al.*[3] showed that pain-producing substances and vaso-active amines, e.g. acetylcholine, serotonin, histamine, bradykinin and neurokinin, could act—either individually or together with local enzymes—by altering the permeability as well as the lumina of blood vessels, and could be involved in the production of vascular headaches.

In 1960, Graham[4] pointed out the structure-activity relationship between lysergic acid, its derivatives, and ergot alkaloids. His observations led to pharmacological testing and clinical trials of certain lysergic-acid derivatives acting as strong serotonin antagonists.

An *ad hoc* committee appointed to classify headache (1962) drew up a classification,[5] the first class of which has been labelled 'vascular headache of migraine type' and is subdivided into 5 sub-categories:

(*a*) 'Classic' migraine.
(*b*) 'Common' migraine.
(*c*) 'Cluster' headache.
(*d*) 'Hemiplegic' and 'ophthalmoplegic' migraine.
(*e*) 'Lower-half' headache.

In this paper, headaches falling mainly into class (*a*) are described.

Classic Migraine

Although many patients show extraordinary changes in weight and marked oedema in the pre-headache stage, diuresis, produced by a strong diuretic, does not prevent nor does it alter the severity of such attacks. Local scalp oedema, present during headaches, can occur unrelated to general oedema.

Vascular headaches may be unilateral or bilateral, or may fluctuate from side to side. The pain may be generalized, affecting the entire cranium, or localized to small areas, sometimes extending only over the upper molars and premolars.

The migraine type of headache is a biphasic vasomotor imbalance. The first phase is one of vasoconstriction—before pain is experienced—when electro-encephalographic tracings may show cerebral ischaemia, occasionally associated with prodromata such as scotomata, and oculomotor, nasal, gastro-intestinal and psychic disturbances. This phase is followed by the actual pain, when there is a change to marked extracranial vasodilation with pulsation and throbbing, usually accompanied by nausea and vomiting.

Many trigger mechanisms are known, and almost any psychological factor associated with stress and strain—and the anticipation as well as the experience of frustration—is common to most cases.

The associated symptoms of autonomic imbalance have occasionally led to faulty diagnosis and to treatment of these symptoms rather than of the basic causes.

Just before, or at the beginning of the phase of vasodilation, certain substances are often effective in aborting the attack. These are vasoconstrictors of the ergotamine type and noradrenaline, and mechanical pressure exerts a similar but transient relief. Once the painful phase of the attack persists and oedema in the perivascular regions develops together with thickening of the vascular wall, response to mechanical pressure and to vasoconstrictor agents is almost lost.

Aetiological Factors

The migraine type of headache is numerically one of the commonest, accounting for more than 70% of all cases of vascular headaches.

A number of exogenous substances have been blamed for vascular headaches, but neither diet nor the withdrawal of the substance concerned improved many patients for any length of time. Exposure tests, such as the administration of the substance theoretically implicated (for instance, chocolate), have not proved successful in producing the headache. The psychological factors—stress, strain, frustration and tension—by themselves were found to be trigger mechanisms rather than true aetiological agents.

It is reasonable to presume that probably all factors mentioned are contributory in a cyclic way, in certain types of personalities, towards producing the migraine type of headache. Wolff[6] formulated the term 'relation of life's situations' for the personality features and reactions in the migraine syndrome. He showed that childhood adjustments, ambition and success, perfectionism and efficiency, orderliness, inflexibility, and resentments, as well as many social and sexual adjustments, are all part of the underlying personality picture of the established migraine sufferer.

In view of the large number of aetiologically interlinked factors, it may appear a little difficult to propose a basic treatment rationale related to local neurohumoral factors alone. It is not the intention of this paper to do so, but since neurohumoral factors play a large part in the full development of the migraine picture, it was felt that if the aetiological factor cycle could be broken at one of

its stages the frequency as well as the severity of the attacks might be alleviated.

SEROTONIN AS A POSSIBLE AETIOLOGICAL FACTOR

One of the metabolites and vaso-active amines mentioned above was 5-hydroxytryptamine (5-HT), generally known as serotonin.

It has been shown that 5-HT, but not isotonic saline of identical pH and volume, could induce low-intensity headaches. Intravenous infusion of 5-HT, carried out for periods of 10 - 20 minutes, induced headaches indistinguishable from the usual head pain complained of by established migraine sufferers. At the same time, this experiment showed that 5-HT caused disagreeable respiratory, gastro-intestinal, nasal and occasionally other vasomotor side-effects.

The hypothesis derived was that 5-HT could be implicated because of its local vascular effects, in addition to being a central trigger agent in migraine headache causation.[7] Serotonin has therefore recently been suggested as a possible endogenous humoral agent which might be therapeutically antagonized in order to break the vascular headache mechanism cycle. It was reasoned that serotonin antagonists might be usefully employed in interval treatment, and, in some cases, in the early acute migraine attack phase.

Idiosyncrasy to 5-HT, sensitivity, and imbalance of the ergotropic-trophotropic[7] mechanism—which is influenced by cerebral 5-HT levels—may be the key to at least part of the physiological mechanism of migraine.

PHARMACODYNAMICS OF SEROTONIN

5-HT has central and peripheral pharmacodynamic effects.

The peripheral effects are better understood than the central ones; it is not quite clear if 5-HT is physiologically effective in its intracellular (bound) form, or only in the free extracellular form. (One of the main workers on this particular problem is Brodie.[7,8])

The actions of 5-HT are summarized below to simplify understanding of its relationship to the aetiology of vascular headaches.

Exogenous 5-HT

When the substance is introduced directly into the brain, or into the circulation in the form of its precursor, 5-hydroxytryptophan (5-HTP), which has the ability to cross the blood-brain barrier, the following pharmacological effects are observed:

1. Oedema production.
2. The exacerbation of inflammatory reactions.
3. Proliferation of connective tissue.
4. Excitement and mania.

Endogenous 5-HT

When large amounts of endogenous 5-HT become liberated, the following pharmacological effects are observed:

1. Increased exudation.
2. Promotion of inflammation.
3. Anaphylactic processes in part. 5 - HT is liberated in certain allergic antigen-antibody reactions.
4. Enhancement of non-specific inflammatory processes evoked by irritant substances (for instance, pleural exudate).
5. Production of pain. The human skin shows increased stimulation of pain nerve-endings in the presence of 5 - HT.
6. Increased intestinal motility. This is due to greater sensitivity of the peristaltic reflex in the presence of 5 - HT.
7. Bronchoconstriction.
8. Circulatory results:
   (*a*) Pulmonary vessel constriction.
   (*b*) Peripheral vessel constriction.
   (*c*) Renal (afferent) vessel constriction.

   Note: Histamine release and certain depressor reflexes are superimposed on general vasoconstriction in some areas; this may confuse the pharmacological picture.

   (*d*) In man, 5 - HT can, therefore, cause a rise as well as a fall in blood pressure, and it is difficult to assign a definitive response factor for these two opposite vascular responses.
9. Anti-diuresis.
10. General stimulation of smooth muscles.
11. Observations following metastasizing carcinoid in man, where large amounts of 5 - HT are produced, throw some light on its peripheral activity:[22]
   (*a*) Erythema.
   (*b*) Flushes and paroxysmal cyanosis.
   (*c*) Diarrhoea.
   (*d*) A bronchial asthmatic picture.
   (*e*) Polyarthralgia.
   (*f*) Heart-valve distortion (tricuspid stenosis and regurgitation).
   (*g*) Peripheral vasoconstriction.
12. Oxytocic action of 5 - HT has been proved in the isolated uterus only.
13. Central nervous system. Areas of greatest autonomic activity show the largest amount of free 5 - HT and 5 - HTP. They occur together with:
   (*a*) Decocarboxylase and probably aldehyde dehydrogenase.
   (*b*) Monoamine oxidase.
   (*c*) Piridoxate phosphate (vitamin B_6 analogue).
   (*d*) Tryptophan.
   (*e*) High noradrenaline levels (often).

   Note: The actions of 5 - HT are a little confusing, because high levels of the substance, produced by intrathecal injection of 5 - HTP, cause psychotomimetic effects similar to lysergic acid diethylamide, with marked sympathetic overactivity, exemplified by:
   (i) Rage, excitement, restlessness and fear.
   (ii) Loss of reflexes.
   (iii) Disorientation and tension.
   (iv) In man (in intermediate doses) mood elevation, but in animals only marked motor activity (which is probably the equivalent).

   On the other hand, Brodie showed that 5 - HT influenced the trophotropic section of the autonomic system causing:
   (i) Sedation.
   (ii) Hypnotic potentiation (blocked by lysergic acid diethylamide).
   (iii) Depression of spontaneous activity.
   (iv) Electro-encephalographic pattern of the sleep type.

Reserpine produces depletion of 5-HT in brain cells, causing trophotropic action, e.g. depression. On the other hand, lysergic acid diethylamide, a strong 5-HT antagonist, causes ergotropic action.

It is concluded from these two facts that 5-HT is a primitive synaptic transmitter of the parasympathetic section of the autonomic nervous system (ANS). It is therefore directly responsible for trophotropic activity. Brodie

stated that in the same way as the ANS activity displays a cholinergic section and an adrenergic section, one should accept a serotonergic section as well. According to him, 5-HT activity, as a primitive synaptic transmitter, strongly stimulates the parasympathetic part of the reticular formation and produces trophotropism comparable to reserpine depression.

Lysergic acid diethylamide inhibits the synaptic effect of this transmitter (5-HT), thereby causing sympathetic-unopposed overactivity or ergotropism.

This mechanism, and the central position of 5-HT in the fine balance of the two sections of the ANS, namely sympathetic-ergotropic and parasympathetic-trophotropic, led to the hypothesis that 5-HT antagonism may have two direct effects in the migraine syndrome:

1. Peripherally, owing to the above described pharmacological effects.

2. Centrally, owing to the lowering of central 5-HT predominance in the autonomic parasympathetic sector.

If this hypothesis is accepted, serotonin antagonism would not only produce neuronal transmission-factor depression in the migraine headache cycle but, owing to its effect on the reticular formation centrally, it would also cause a better 'balance' of the two sections of the autonomic nervous system. Since it has been shown that autonomic imbalance can be presumed to be one of the aetiological cycle factors of the migraine-type headache syndrome, 5-HT antagonism may present a cycle break.

CHEMISTRY AND PHARMACOLOGY OF THE SEROTONIN ANTAGONIST UML-491

1-methyl-D-lysergic acid butanolamide (known as UML-491 or 'deseril') is a strong serotonin antagonist.[9] For convenience, it will from now on be referred to as UML-491.

The chemistry of UML-491 is shown in Fig. 1.

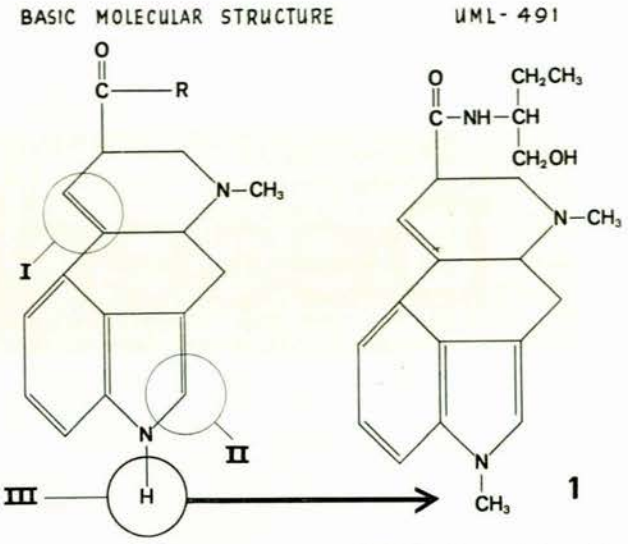

Fig. 1. Showing the chemistry of UML-491, and how it is formed from the basic molecular structure of lysergic acid compounds. The ways in which this molecular structure is altered are as follows (Roman numerals refer to numbered circles):

I. Saturation of double bond C_9 - C_{10}, giving dihydroalkaloids (DHE-45, 'hydergine').

II. Halogenation in position 2, giving 2-brom derivatives (BOL-148, 2-brom ergotamine).

III. Alkylation in position 1, giving 1-methyl derivatives (UML-491, 1-methyl-ergotamine), as in the figure.

The chemistry of UML-491 (deseril) is as follows: 1-methyl-D-lysergic acid butanolamide, $C_{12}H_{27}O_2N_3$; molecular weight 353; salt—bimaleinate.

General remarks concerning UML-491:

1. It is a 1-methylated derivative of lysergic acid which exhibits strong antiserotonin activity.

2. The pharmacodynamic effects are considerably reduced or abolished by alkylation of lysergic acid compounds in position 1, with the exception of the serotonin antagonism in the 1-methyl derivative.

3. The parent compound, butanolamide of lysergic acid, has been used for many years in obstetrics and gynaecology as a uterotonic. By methylating the indol-nitrogen of the molecule, a compound with entirely different properties is obtained.

Comparison of Serotonin Antagonists

Table I shows that all the tested substances (with one exception) have a comparatively greater activity *in vitro* than *in vivo*, if lysergic acid diethylamide (LSD) is taken as a standard. (The exception is UML-491, which displays equal potency both *in vitro* and *in vivo*.)

TABLE I. SEROTONIN ANTAGONISTS COMPARED*

Test substance	*Antiserotonin activity (LSD=100)*	
	In vitro (isolated rat uterus)	*In vivo (serotonin oedema in the rat's paw)*
D-lysergic acid diethylamide (LSD)	100	100
2-bromo-LSD (BOL-148)	103	29
1-acetyl-LSD (ALD-52)	210	
1-methyl-LSD (MLD-41)	368	
1-methyl-bromo-LSD (MBL-61)	533	26
1-methyl-D-lysergic acid butanolamide (UML-491)	400	440

* After Cerletti and Doepfner.[10]

Studies with highly active serotonin inhibitors revealed a finding of therapeutic interest, viz. that there is no correlation between peripheral antiserotonin activity in animals and psychic effects in man. This is particularly true of UML-491, which has hardly any influence on the psyche, although it is four times more active at the periphery than LSD.

Pharmacological Actions of UML-491

1. Serotonin antagonism. If lysergic acid diethylamine=100, then UML-491=400.

2. LD_{50} mg./kg. intravenous:

(*a*) In mice: 85.

(*b*) In rabbits: 2·6.

(*c*) In rats: 23.

3. Blood pressure. There is a progressive lowering of the blood pressure, with passive decrease of renal volume. There is a slight increase in the pulse rate when the systolic blood pressure is lowered by about 20 mm.Hg.

4. Transitory vasoconstriction in the limbs.

5. A transitory drop of cephalic venous pressure without any influence on the systemic intra-arterial blood pressure.

6. Barbiturate (specifically 'sodium pentothal') and alcohol potentiation.
7. Oxytocic activity—mild and only relevant during the 3rd trimester.

Side-effects of UML-491

1. Loss of power to concentrate.
2. Lightheadedness and/or lassitude.
3. Mild disorders of perception.
4. Nausea and vomiting.
5. Feeling of depersonalization.
6. Peripheral vasoconstriction.

Note: These effects do not occur in many cases and appear to indicate a degree of idiosyncrasy. They are, however, dependent in all cases on dosage. It appears that a degree of tolerance to the side-effects develops in most patients who persevere in the use of UML-491 after the initial discomfort. Tolerance to the therapeutic effect does not appear to develop to an equivalent degree, and a reduction of dosage has proved a satisfactory therapeutic measure when side-effects have occurred.

Dosage

Doses up to a maximum of 8 mg. daily have been given. However, satisfactory response to interval treatment for the migraine type of headache has been achieved with as little as 2 mg. daily by mouth.

Contraindications

1. Pregnancy.
2. A thrombotic tendency.
3. Coronary and peripheral vascular disease.

CLINICAL PILOT TRIAL OF FIVE CASES

In view of the fact that good results following the use of UML-491 have been described in several countries, it was decided to collect five cases of migraine-type headache in Johannesburg, since local factors such as climate, stress and strain, mine dust, flora, electric storms, altitude, and many others, must all be considered as either possible trigger mechanisms or, at least, predisposing factors.

The cases and results are summarized below.

Case 1

Male, 46 years of age.
Medical history: not relevant.
Surgical history: tonsillectomy, appendicectomy, cholecystectomy.
Weight: 8 kg. overweight for height and age.
Physical examination: no detectable abnormality in any system.
X-ray chest and sinuses: normal. (The X-ray age of the patient was ±40 years.)
Electrocardiogram (ECG): normal.
There is a family history of migraine attacks (mother and sister).

Migraine History

The patient himself gives a history of various vascular headaches since puberty; increase of attacks up to the age of 36; thereafter, a decrease in severity and frequency. During the last 4 or 5 years attacks were related mainly to stress, strain and frustration. These attacks did not follow but rather appeared before the event, e.g. when the patient was aware that he would be made subject to trigger factors. He is a professional man with marked perfectionist tendencies, exhibiting great drive and carrying responsibilities. Recently, most of his symptoms have become rather more abdominal and his physician calls the syndrome abdominal migraine. The symptoms include:

1. Increase in weight.
2. Water retention.
3. Gastro-intestinal hyperactivity (secretions and motility).
4. Diarrhoea.
5. Cold extremities and general skin vasoconstriction.
6. Feeling of vaguely described but acutely felt general discomfort.
7. Dry mouth and throat.
8. Feeling of heat in the head.
9. Foetor oris which is invariably present before the attack.
10. Mild headaches with loss of power of concentration.
11. A distinct period of 'well-being' before the attack.
12. At the end of the attack usually marked diuresis and mild constipation.

The attacks last approximately 4 - 12 hours. Occasionally, there is a classical migraine-headache attack without abdominal symptoms, with prodromata and severe unilateral headache, but no vomiting. These last up to 48 hours.

Frequency

Classical migraine—more or less every 14 days.
Abdominal migraine—more or less every 3 - 5 days.

Treatment

UML-491 (deseril) was given, using 1 mg. tablets. Treatment began with 2 tablets *statim*. This produced marked disturbance of perception and loss of ability to concentrate. Thereafter, the patient was put on the following regime: 1 mg. for 2 days, 2 mg. for 16 days, 3 mg. for 12 days, 4 mg. for 24 days, 3 mg. for 24 days, and 2 mg. maintenance dose for about 3 months (in divided oral doses).

Results

During the time of treatment there was no attack of classical hemicranic vascular headache. The abdominal attacks were reduced in frequency to more or less 1 every 10 days and the severity of the attacks was considerably reduced.

The patient stated that he had not felt so well nor been so free from headaches as long as he could remember. UML-491 was stopped after about 5 months. The patient now takes 1 mg. *b.d.* occasionally, when he feels an attack starting. This, combined with 10 mg. of chlordiazepoxide, usually aborts the attack.

He is a good observer and reports meticulously on his condition. By his own judgment he considers treatment a success.

Case 2

Female, 40 years of age, married.
Medical history: not relevant.
Surgical history: nil.
Obstetrical history: gravida iv, para. iii. All pregnancies and deliveries normal.
Gynaecological history: menstrual periods normal and regular.
Weight: normal for age and height.
Physical examination: no detectable abnormality in any system.
X-ray chest and sinuses: normal.
ECG: slight left-axis deviation, otherwise normal.
No family history of headaches.

Migraine History

The patient gave up a career to get married. She began to develop a variety of vascular headaches, interspersed by rather frequent classical migraine attacks with fortification aura.

The onset was at the age of about 28 years, 4 years after her marriage to an over-solicitous husband who persuaded her to see physician after physician for fear that she had 'cancer of the brain'.

The patient ran a perfect home and was a good mother. Yet she had strong feelings of general inadequacy and frustration because she felt she should not have given up her career. Sexual adjustment was not good at any stage of this marriage.

Frequency and Duration

Every 3 - 5 days she had a classical migraine attack with

prodromata, occasional vomiting, and intense one-sided pain, pulsating in nature. The frequency of attacks was less during some periods of her married life. She then used to complain of headaches which were not typically migrainous and less severe. This pain was relieved by aspirin, phenacetin and caffeine combinations, but not completely. These preparations had no effect on the frequency of attacks.

The classical migraine attacks were not much influenced by any preparation. Ergotamine tartrate, by injection, would occasionally abort the attack if given early during the prodromal phase, but not invariably so.

Average duration of 'ordinary' headaches was 3 - 6 hours, but the classical migraine lasted 12 - 72 hours, and relief was always linked to spontaneously occurring diuresis.

Treatment

As far as possible during the interviews any psychotherapeutic approach was strictly avoided. The patient is an intelligent person with a matter-of-fact attitude, and her illness was discussed as being probably due to physical causes only.

Treatment with UML-491 was given according to the following regime: 2 mg. for 6 days, 3 mg. for 28 days, 4 mg. for 3 months, 3 mg. for 1 month, 2 mg. for 15 days (in divided doses). Thereafter, 2 mg. were taken occasionally when required.

Results

During the first month there was no change in the frequency of the headaches. During the second month, one classical migraine attack and two 'ordinary' headaches occurred. During the next 4 months the patient had no headaches. During the fifth month one attack occurred when a difficult home situation was about to arise.

At present, the patient takes 1 or 2 mg. when she feels that a headache is about to begin. She maintains that on approximately 9 out of 10 occasions the attack is aborted or the severity of pain is much reduced and the duration shortened. As soon as proper pain develops she uses a combination of caffeine and ergotamine, together with 300 - 600 mg. of methylpyrazalone ('dipyrone'), which appears to be very effective in her case.

She considers UML-491 treatment a success.

Case 3

Female, 25 years of age, unmarried.
Medical and surgical history: nil.
Obstetrical history: gravida ii, para. 0.
Physical examination: no detectable abnormality in any system.
X-ray chest and sinuses: normal.
ECG: not done.
No family history of headaches—mother, father and two brothers are alive and well.

Gynaecological history: Patient has had fairly violent headaches since puberty with almost every period. Vascular headaches occur quite frequently, usually after ovulation. There are about 2 - 3 headaches during the fortnight before the next period begins.

Weight

Because the patient's body weight fluctuated by as much as 3½ kg. (8 lb.) before menstruation, it was decided to ask her to have urinary sodium/potassium ratios done and to measure aldosterone excretion during a stay in the USA.

The results of these tests were as follows:

1. Lowest aldosterone levels occurred on about the 20th day before menstruation. The average of these lowest levels was 8·1 μg. in 24 hours.

2. The levels rose to 10 μg. daily on the 15th day before menstruation.

3. A continuous rise in the second half of the cycle showed a maximum about the third day before menstruation commenced, when the patient excreted 35 μg. in 24 hours.

4. Thereafter the level dropped precipitously, to the lowest level of 7·2 μg. in 24 hours on the first day of the menstrual flow.

5. The sodium/potassium ratio fluctuated during the cycle, but the relationship between aldosterone excretion and sodium/potassium ratios could not be established:

(*a*) The lowest sodium/potassium ratio was recorded on the third day before menstruation.

(*b*) During the same period aldosterone reached its peak excretion level.

(*c*) Body weight was highest then, and the patient was generally oedematous and felt uncomfortable.

Note: The blood pressure was slightly raised just before menstruation, the patient's normal average being 106/74; at that period it rose to 126/84.

Conclusions

Migraine-type headaches occurred at the lowest sodium/potassium excretion ratio level and the highest aldosterone excretion level. This was usually just after the patient had gained the greatest amount of weight and the blood pressure had, by that time, already risen above her normal average level.

Strain and Stress Factors

These were constantly present with tension, fear and apprehension linked to uncertainty concerning the always eagerly awaited menstrual period. On account of this situation sexual adjustment was poor and often linked to frustration—psychologically and physically—when her 'nervousness' prevented orgasm and relaxation.

Treatment

In view of the stress and strain situation, which was not explained to the patient so as to avoid a psychotherapeutic set-up, UML treatment was initiated jointly with chlordiazepoxide. However, this substance was withdrawn after 76 days and a new treatment period of 70 days was started without any adjuvant therapy, e.g. only on UML-491.

The regime of treatment was as follows: 2 mg. of UML daily combined with 10 mg. of chlordiazepoxide, in divided doses, for 12 days; 3 mg. of UML daily, with 15 mg. of chlordiazepoxide, for 24 days; 4 mg. of UML daily, with 15 mg. of chlordiazepoxide, for 30 days; and 4 mg. of UML daily, with 10 mg. of chlordiazepoxide, for 6 days. Thereafter, 3 mg. of UML alone were used for another 70 days.

Results

Combined therapy of UML and chlordiazepoxide for the first 76 days:

(*a*) Only one episode of classical migraine occurred, but of shorter duration and with very little pain. This was controlled by the administration of aspirin, phenacetin and caffeine, 2 tablets as one single dose.

(*b*) The vascular headaches in the postovulatory period disappeared, with the exception of one attack during the first 14 days of treatment.

Therapy with UML alone over 70 days:

(*a*) No migraine attacks were reported.

(*b*) There was a mild general vascular headache on two occasions, which needed no analgesic treatment and lasted for about one hour.

Although the set of circumstances linked to headache production, i.e. menstruation relationship, weight gain and oedema, tension, fear, and apprehension, had not been treated, and although the life situation of the patient did not change, she reported treatment as successful.

UML-491 has now been withdrawn, but it is too early to report on a possible recurrence, and this patient is now being followed-up.

Case 4

Male, 35 years of age.
Medical history: not relevant.
Surgical history: nil.
Weight: normal for age and height.
Physical examination: no detectable abnormality in any system.
X-ray chest and sinuses: normal.
ECG: not done.
Family history of migraine present in father and mother.

Personality

The patient is a well-educated, intelligent man with strong drives and a responsible industrial job, married. There are two children. His relationship to his wife is good. Sexual adjustment is normal and the marriage appears to present no problem, but acts rather as a haven of peace from his harassing type of work.

Migraine History

The headaches are of the classical migraine type only. The patient does not know any other type of head pain.

Frequency of attacks—2 - 3 every month.

The attacks are brought on by difficult situations which he anticipates in the progress of his work, and when the responsibility which he carries appears to be, at times, too much for him and interferes with his perfectionist tendencies.

The patient has been given a variety of treatments. Among the substances used were ergot alkaloids, aspirin, phenacetin, caffeine, diuretics, phenobarbitone and, during the last 3 years, tranquillizers and hormones.

Every new treatment was initially successful, but attacks usually occurred—even on treatment—within a month.

Treatment

Therapy with UML-491 was given for 5 months—the details of the regime were almost identical to those described in case 1, and are therefore not given here.

Results

During the entire treatment period the patient reported 3 classical migraine attacks, but he remarked that the prodromata, which had normally ushered in the painful period, did not occur. These headaches began—as he expressed it—'out of the blue'. The pain itself was unilateral and less severe than before treatment, and the accompanying symptoms of loss of power of concentration and general autonomic upset were much less. The patient now takes 2 mg. of UML-491 occasionally, when he thinks that a headache is about to occur.

This patient is a good reporter and an intelligent observer of his condition. He considers the treatment with UML-491 a success.

Case 5

Female, 34 years of age, married.
Medical, surgical and gynaecological history: not relevant.
Weight: average for age and height.
Physical examination: no detectable abnormality in any system.
X-ray chest and sinuses: normal.
ECG: normal.

Migraine History

This patient suffers from classical migraine, although she is unable to relate her attacks to life situations, stress and strain, menstruation or any of the other known trigger mechanisms.

Her personality is not perfectionistic and her education and aptitude are average.

Therapy with UML-491: 2 mg. *b.d.*

Results

The patient reported violent psychological disturbances. She was unable to concentrate, could not do her work, felt lightheaded and overexcited. She usually has one whisky in the late afternoon when her husband returns from work. From the day when UML-491 was started, this one drink intoxicated her, a condition which was quite unknown to her before.

She was persuaded to persist with treatment, with an assurance that the side-effects of UML-491 would disappear. The dosage was reduced to 1 mg. per day for 2 days, and then increased to 2 mg. for another 6 days. During the entire 9 days of treatment, the patient was not herself, complaining strongly of the disturbing psychological effect, and finally refused to cooperate.

During treatment with UML-491 she had no migraine attacks.

Conclusion

Success or failure cannot be judged in this case, because the side-effects prevented any assessment of effectiveness.

REPORT ON OTHER TRIALS

A number of authors reported results in groups of patients with conditions subdivided into migraine and Horton's syndrome. The results reported by these workers are given in Table II.

CONCLUSION

In view of the successful results of treatment with UML-491 in at least 4 of the 5 pilot cases described, as well as the successful reports that have appeared in the literature in other countries, it is suggested that a double-blind therapeutic trial might well be conducted on a large series of patients to confirm the findings of the above pilot trial, although the problem that such a double-blind trial would present is considerable.

From the observation of the cases described, it cannot

TABLE II. RESULTS OF OTHER TRIALS

	Migraine				*Horton's syndrome*			
	Total	++	+	—	*Total*	++	+	—
Sicuteri[11]	18	9	9	–	2	2	—	—
Heyck[12]	24	2	16	6	8	8	—	—
Friedman[13]	23	2	16	5	3	2	—	1
Dalsgaard-Nielsen[14]	30	16	6	8	—	—	—	—
Harris[15]	45	30	5	10	5	5	—	—
Rooke *et al.*[16]	47	30	5	12	49	41	2	6
Abbott[17]	39	20	12	7	3	3	—	—
MacGregor[5]	16	13		3	10	9		1
Graham[18]	76	55		21	20	16		4
Friedman and Losin[19]	150	97		53	21	15		6
Hale and Reed[20]	33	23		10				
Ekbom[21]	41	26		15	4	—	—	4
Total	542	392 (++/+) (72%)		150 (—) (28%)	125	103 (++/+) (82%)		22 (—) (18%)

++=very good response, +=good response, —=poor response.

be stated categorically that UML-491 was solely responsible for the apparently good result, because migraine-type headaches are subject to a number of aetiological factors and trigger mechanisms. The paper has been presented as a suggestion of how the headache-mechanism cycle might conceivably be broken if the hypothesis that serotonin is responsible for a number of vascular headaches is acceptable.

Furthermore, that serotonin antagonism is desirable in the therapeutic approach to vascular headaches requires further investigation, as does the 5-HT—headache relationship.

SUMMARY

1. A short survey of migraine-type vascular headaches is presented.

2. The question whether serotonin is a neuro-humoral aetiological agent is discussed.

3. The pharmacodynamics of serotonin are enumerated.

4. The chemistry and pharmacological actions of a serotonin antagonist, methysergide, are listed.

5. Five pilot trial cases treated with methysergide (UML-491, deseril) are reported.

6. A suggestion that serotonin antagonism may be useful in breaking the headache cycle is made, and reasons for further investigation and double-blind trials are suggested.

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