nates the excitement period, assures better control of anæsthesia, procures good muscular relaxation, diminishes postoperative nausea, vomiting, pulmonary and gastrointestinal complications; and has less toxic systemic effect than ether. Most important, it permits use of the two agents without fear of giving a toxic overdose of either.

We have been using this combination for several years and have had excellent results with it. While not a perfect combination, we are convinced that it is an advance in anæsthesia.

MIGRAINE: ITS TREATMENT WITH PROSTIGMINE BROMIDE*

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THE pain of migraine headache can be excruciating, even forcing the sufferer to thoughts of suicide, yet few physical signs can be made out to substantiate the patient's complaint. To attack a disease intelligently, its etiology must be known, and the fundamental cause removed, if possible. Failing this, the next best approach is through a study of its pathological basis, both anatomical and functional, with a view to correcting the disturbance. This appears to be the course which we must follow with migraine. In the present attempt to do so, none of the statements which follow are new, but the picture which they present, and the conclusions to which they lead, may help to clarify the problems of causation and treatment.

The anatomical pathology of migraine need not detain us. In the nature of things, it is and must remain obscure, since patients do not die of an attack, and what changes there may be are transitory and reversible.

We have first to note its resemblances to epilepsy and to allergy. All three appear to have a constitutional factor, a diathesis, although different regions or systems are selected as the point of attack. In the family and personal history of patients suffering from any one, there is a high incidence of the other two. In all, there are indications of nervous imbalance. The relation of epilepsy is the least clear-cut, and many observers deny that it is a migrainous or allergic equivalent, but it is at least suggestive that both epilepsy and migraine exhibit the same four stages—prodromata, auræ, attack, sequelæ—and that all three types of attack can be precipitated by mental tension or emotional strain.

It should not be concluded that migraine is allergic in nature. Only rarely can a specific allergen be incriminated. The point to be made is that there is in each a fundamental neurovascular dysfunction. Hormonal imbalance is often found in both conditions, and the influence of menstruation, pregnancy, and the menopause is undisputed.

The above considerations would suggest that a similar mechanism is responsible for both types of attack, and perhaps for epilepsy as well, and it is possible that this mechanism may be either an abnormally facile release of histamine-like (H–) substance, or an abnormal sensitivity to it. Histamine, generally distributed in normal cells, is ordinarily inert, but when released, by appropriate methods, into the tissue fluids, has an intense vasodilator action.

Goltman divides the mechanism of the migraine attack into three stages: (1) Vasomotor spasm, leading to temporary ischæmia of parts of the brain, causing the aura. (2) Secondary vasodilation, with resulting œdema of the brain, causing headache. (3) Temporary hypersecretion and hyperabsorption of spinal fluid, tending to equalize the intracranial pressure, and producing the polyuria which is frequently noted among the sequelæ.

One can hardly fail to note the resemblance to the so-called "triple response" to intradermic histamine injection: vasodilation (red flush of skin), followed by increased permeability and local œdema (wheal).

On the other hand, Hare and Cushing consider the pain of migraine to be caused less by disturbances in the cerebral vessels than by dilation of the cranial arteries, particularly the branches of the external carotid. A point in favour of this view is the relief of migraine headache, when the amplitude of pulsation in the temporal arteries (and therefore in the other branches of the external carotid) is reduced by digital pressure on the carotid artery of the affected side. The effectiveness of injection of ergotamine tartrate, which acts in a similar manner on the vessels, also bears out the contention of Hare and Cushing.

Both hypotheses explain some of the observed phenomena, but not all. I should like to venture

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the suggestion that both may be substantially and simultaneously correct. The combined hypothesis would postulate the following events:

1. Angiospasm, of both intra-cerebral and extra-cerebral intracranial arterioles, raising pressure in the corresponding arteries, and leading to

2. Vasodilation of both cerebral and meningeal arteries, followed by exudation, increasing the pressure both inside and outside the meninges. It is possible that spasm persists in the arterioles, enhancing this effect.

3. Hypersecretion and absorption of cerebrospinal fluid, slowly restoring cerebral pressure to normal and terminating the attack.

4. Where ergotamine tartrate is exhibited, its action is two-fold. It causes constriction of the dural arteries, and it relieves spasm in the cerebral arterioles, due to sympathetic inhibition. The cerebral blood-flow is thus increased and the removal of exudate hastened. That ergotamine tartrate does produce these effects on the intracranial blood-vessels has been shown by Pool and Nason, while Lennox, Gibbs and Gibbs have demonstrated a moderate, prolonged increase in cerebral blood-flow, following ergotamine tartrate administration.

The idea of the primarily angiospastic character of migraine is corroborated by two facts: first, the similar origin of other manifestations preceding, accompanying, or at times replacing the headaches: *e.g.*, scotomata, pallor, myalgia, dizziness, hypertension, even occasionally hemiplegia or aphasia; and, second, the abortion of an attack in the preliminary stage, or its relief when established, by the spasmolytic action of ergotamine tartrate or intravenous papaverine hydrochloride, or oral carbachol.

The, perhaps rash, assumption, that the similarity of the above-suggested mechanism to allergic reactions and to the effects of histamine might indicate a line of therapy, led to the consideration of histamine desensitization. However, in view of the number of annoying injections needed, the danger of reactions, the cost to the patient, and the inconclusive results hitherto reported on histamine desensitization for allergic conditions, it was felt that an oral substitute would be highly desirable, could an effective one be found.

Prostigmine bromide fills the bill here. Its action as a parasympathetic stimulant, inhibiting the action of cholinesterase, produces vasodilation of peripheral vessels, chiefly arterioles; it is highly effective by mouth; and its cost, in the dosages needed is ludicrously low. A few years ago, Pelner and Aibel accidentally discovered that oral desensitization by prostigmine was effective in a case of histamine headache, and later found similar results in headaches of the migraine and hypertensive types.

In a recent series of six patients of my own, with histories of migraine of from 8 to 25 years' duration, the response to prostigmine was similar: 2 reported moderate improvement, 3 marked improvement, and 1 declared it was "a miracle".

The technique of treatment is as follows: One 15-mgm. tablet of prostigmine bromide is dissolved in an ounce of distilled water. The patient is instructed to take it three times daily, beginning with one drop, and increasing by one drop each dose, until she is taking 10 drops three times a day. After continuing at this dosage for 1 week, she drops to a maintenance-dose of 10 drops twice weekly, and if any signs of impending headache are noticed, takes an additional 15 to 20 drops.

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THE ROLE OF RIBOFLAVIN IN MIGRAINE

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THE artificial synthesis of riboflavin was first accomplished in 1937, and with an adequate supply for clinical investigation available, it was not surprising that certain syndromes became early identified as due to ariboflavinosis. The intervening years have but served to prove the accuracy of these observations.

In 1939, Spies, Bean and Ashe[1] described eye lesions characterized by burning sensations, conjunctivitis, lachrimation and failing sight, some of which responded to riboflavin, and a year later, Spies, Bean, Vilter and Hubb[2] described the same eye signs and, in particular, a peculiar violet congestion of the conjunctival vessels. They noted that these symptoms re-