MIGRAINE—THE MENSTRUAL ASPECT

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I am afraid that I have nothing new to say and I therefore rise to address you with some diffidence. Apart from a few speculations which I shall introduce before the end, everything I have to say was published by Dr K. Dalton and myself in 1953. However, recapitulation may not be valueless, because I do not think our paper has had quite the good result it might have had. It may be a good thing to bring forward our results again in this symposium.

Migraine is often a part of the premenstrual syndrome from which about 30 per cent of women suffer one way or another to a greater or lesser extent. The commonest form of the syndrome is a minor endocrine disorder which most women accept as part of the business of being a woman. When the syndrome includes migraine it becomes serious.

With Dr Dalton I reported 84 severe cases of the premenstrual syndrome. Of these 58 had headache and of these 49 had classical migraine at times. It would be unwise to be statistical about such a small series, but it looks as if about 20 women in every 100 suffer sometimes from premenstrual migraine. They very often do not realize the relationship between the migraine and menstruation because, although the attacks occur always at mid-cycle or premenstrually, they do not occur in every month. The common feature is that the intervals between the attacks are multiples of two weeks. If you get every woman who complains of migraine to keep a diary of her attacks and her periods it becomes clear that when migraine does occur it is nearly always at ovulation time or just before a period. De Witt estimated that 60 per cent of female sufferers have migraine of this type. The onset of the period brings in most cases complete relief. Pregnancy also brings complete relief, though afterwards the trouble may recur with increased severity.

There is often a family history of migraine, not necessarily premenstrual and, indeed, not necessarily in the women only of the family. It would appear that there is an underlying tendency to migraine, which is " triggered off " premenstrually by an unknown

factor which operates at this time.

What is this factor? We know that migraine in general may be precipitated by many different things, including mental stress, from which many women suffer before their periods, but I have not observed any relationship between such stress and the occurrence of migraine, and sedatives are rarely helpful. Fluid retention is known to precipitate attacks in both sexes and an increase in weight due to fluid retention is usual premenstrually: sometimes it is excessive, amounting to as much as a stone. But when one considers the hypothesis that premenstrual migraine is due to excessive accumulation of fluid, one is faced with the fact that there is not a very close correlation between water-retainers and migraine-sufferers. Moreover I have recorded the individual case of a patient with both water-retention and migraine who did not necessarily have her attacks when her weight was highest. Elimination of premenstrual water-retention by diuretic drugs does not always relieve migraine. Rise in weight is commoner at mid-cycle than before the period, but migraine is commoner before the period. So this beautiful hypothesis has a lot against it.

Supposing, as I think, that premenstrual water retention does account for many cases, we must consider why it occurs. Mid-cycle and the premenstruum are the times when the secretion of oestradiol is highest. Oestradiol is a potent antidiuretic substance. Progesterone has an anti-oestrogenic effect. The hypothesis has therefore been advanced that the cause of the whole premenstrual syndrome is an excessive oestradiol/progesterone ratio. In support of it is the undoubted fact that a high proportion of women can be relieved by injections of progesterone, but this proves nothing. There are other possibilities.

For instance, the adrenal cortex, with its potent controlling influence over salt and water metabolism, might be involved. It secretes aldosterone which retains salt and water; and, be it noted, progesterone has an action opposed to aldosterone. I am speculating rather wildly, because little is known about cyclical changes in aldosterone secretion. This suggestion has not been studied because at present aldosterone determination cannot be done in my laboratory, but I have taken a short cut and treated two patients, in whom all other attempts had failed, with spironolactone, and with complete success. But this proves nothing. The success may have been due to the psychological effect of therapeutic enthusiasm. The subject needs much further study and one requires only money to reach a conclusion.

Meanwhile there remains treatment by the intramuscular injection of 25 mg. of progesterone on alternate days in the luteal phase.

If this works, the implantation of 500 mg. of progesterone should be considered for the effects last for several months. Dr Dalton and I reported the results of 38 cases of premenstrual migraine treated with progesterone. Of these 32 were completely relieved (84 per cent). It is interesting that of 33 patients treated with ethisterone, only 16 were completely relieved (48 per cent). In the light of work done since at New End Hospital I have no doubt that this was a " placebo effect ". I think, however, that there can be no doubt that the majority of patients suffering from premenstrual migraine are satisfactorily relieved by a sufficiently large dose of progesterone, and the main object of my being here today is to impress this fact upon you. I know from letters 1 have had from general practitioners that this is not yet generally recognized.

REFERENCE

Greene, R. and Dalton, K. (1953) *Brit. med. J.*, **1**, 1007.

LOCAL FACTORS IN THE CAUSATION OF MIGRAINE

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I should first like to say that I have myself had migraine, and the circumstances in which I remember it starting were when the Middlesex Hospital Medical School moved to Bristol during the first period of the war. I remember one day trying to read some chemical formulae and finding that I could not see when I looked straight at them but that I could see if I looked out of the corner of my eye. Then things began to shimmer. Finally, I got a headache on one side. That happened quite frequently during the first three years of the war. In 1942 I married and since then I have only had four attacks!

I want to talk first about the sort of things which you might expect from a pharmacologist, but from a pharmacologist looking at the subject from the point of view of investigation rather than from the point of view of treatment. What I propose to do is to discuss one or two aspects of the local manifestations of the migraine syndrome and to consider which mechanisms may underlie their production.

I will refer first to the central scotoma and other visual manifestations in the prodromal stage. J. R. Graham and H. G. Wolff (1937)