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

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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)

made some interesting observations on this aspect. They showed that this was likely to be due to vasoconstriction either in some appropriate part of the brain or possibily in the retina, and their evidence in favour of this was the fact that if during the actual development of a scotoma a patient inhaled amyl nitrite in a dose which would cause vasodilation without any significant effects on the blood pressure, within a quarter of a minute the scotoma was abolished. As the effects of the amyl nitrite worked off, so the scotoma returned. If, on the other hand, amyl nitrite was taken in a dose which lowered the blood pressure markedly, that seemed to have only a very brief initial effect and when the blood pressure fell the scotoma came back. The inference from these observations was that there was some cerebral vasoconstriction probably in the visual cortex. These visual phenomena usually end before the headache comes on. It therefore seems that in some cases at least there is a likelihood of an initial period of vasoconstriction affecting intracerebral vessels, and that might account for effects upon motor functions as well.

When we consider the mechanism of the headache, it seems that we are dealing with some quite different phenomena. I would not like to say how far the investigations which Dr Harold Wolff and his colleagues made were representative of cases as a whole, but certainly the evidence which they provide from the cases which they have studied is pretty convincing. Wolff's view was that the headache was related to vasodilatation affecting the branches of the external carotid artery, and the evidence in favour of this view came from observations in which he recorded the amplitude of pulsation of the temporal and occipital arteries. He also recorded intracranial pressures by measuring the cerebrospinal fluid pressure in the lumbar region. These changes were correlated with subjective estimates of the headache. Initially there was a high amplitude of pulsation. Then 0.4 mg. ergotamine tartrate was given intravenously and the amplitude of the pulsation was reduced. As the amplitude was reduced, so the headache diminished and there seems to be a close parallel between the two events. On that basis he has ascribed the relief of the headache to reduced amplitude of the pulsation. That is the sort of basic effect which apparently occurs in some cases, a rise of blood pressure and reduced pulsation. One can suggest that the relief is due to the reduced expansion of the artery with each pulse.

That brought things into line with what had been shown in respect of the headache produced by intravenous injection of histamine. In this case you get dilatation of vessels, probably meningeal vessels, or at any rate vessels within the skull. By raising the cerebrospinal fluid pressure you can diminish the amplitude of arterial

pulsation and relieve histamine headaches. The relief of migraine headaches comes about through reduced amplitude of the temporal arterial pulsations. This is confirmed by the fact that if you apply pressure to stop the pulsation in a particular branch of an artery supplying a region in which there is a headache, that, too, alleviates the headache.

This action of ergotamine occurs with small doses, and in order to see whether it is purely an effect of the vasoconstriction one can produce vasoconstriction by other means. Wolff and his colleagues showed that if you give an infusion of noradrenaline you get the same sort of effect. The blood pressure is raised by noradrenaline. The diameter of the vessels gradually diminishes after a while and the intensity of the headache also diminishes. At the same time the deep-pain threshold has been measured by a pressure algometer. Over the region in which the headache occurs this is at first low but rises after the vasoconstriction. These observations confirm that vasoconstriction will relieve the headache.

It was also noted that in many cases there was local oedema on the side of the headache so that the full picture can be described as one of dilatation, increased arterial pulsation in the affected side, oedema, and a reduction of deep pain threshold.

If this is the true situation, the question naturally arises as to what mechanisms are involved. Can it be through any sort of unitary process or must we ascribe the vascular effects and the pain threshold effects to different processes? I will suggest that it may be possible to explain them in terms of a single reaction, but this will involve an element of speculation.

In order to study this point more closely, Chapman and Harold Wolff and their colleagues did some experiments in which they collected fluid from the part of the head in which there was a headache. They injected about 2 ml. of saline into the subcutaneous tissues, and after a short while withdrew as much of the fluid as they could. They tested this for the presence of certain agents which I will mention in a moment, and they found that they could recover a pain-producing material in the fluid which they withdrew from the side on which the headache occurs. When they injected saline into the normal side and withdrew it and tested it, they could not find evidence of the same substance being present.

That naturally raised the question of what this substance might be, but before going further I should like to show how this work of Wolff and his colleagues linked up with the work with which I have been concerned with my colleagues at Middlesex for some ten years. What we have done is to study possible pain-producing agents

which might occur naturally within the body. We came to do this partly on some theoretical grounds, but we became particularly interested in it when we had done certain experiments. In trying to test the capacity of substances to produce pain we raised a blister on the skin of the forearm. We then took out the fluid and removed the top. If you drop solutions of substances capable of causing pain on the exposed nerve endings in a blister base, they will cause pain.

When we were doing this work, on one occasion we took out the blister fluid and withdrew it as we always did into an ordinary tuberculin glass syringe. We left it for 20 minutes and we were using it as a control fluid which we thought should be inert. But when we put it back we got quite marked pain from it. We began to look into the phenomenon and found that all sorts of exudates did it and blood plasma too, and that the process which caused the activation was the contact with glass in the course of withdrawal, which suggested a relationship with blood clotting.

What we eventually found was that this phenomenon was probably due to the formation in plasma, serum, or exudate of a substance which is polypeptide in nature and which belongs probably to a small group of compounds which have been given the generic name of plasma kinins. One of these is bradykinin, a polypeptide, which is probably formed by enzymic action. We suggest that in withdrawing these fluids into the glass syringe a process occurs which is similar to that occurring in the body. We have done a lot of work which suggests that where we have damaged tissue we have activation and the plasma kinin so formed will lead to the production of pain and also to the production of vasodilatation and increased capillary permeability.

Wolff and his colleagues have referred to oedema fluid which occurs locally, an accumulation which constitutes a form of inflammation. It is not of bacterial origin. They have studied the fluid and they have found that it contains a substance like bradykinin, but they found certain differences in the way in which it affects smooth muscle preparations. It is depressor in the rat. They call this substance "neurokinin" implying that it is an agent which is formed by nervous activity. They have done further work which shows that antidromic impulses cause release of this neurokinin. They also claim that neurokinin is released in axon reflex responses in the skin.

I do not say that we agree entirely that this substance of "neurokinin" is necessarily different from the plasma kinins about which I have spoken and which many investigators have been studying in recent years. It is likely that Chapman and Wolff have been dealing with a mixture of something like bradykinin with other substances

which would also be released from damaged tissues. But it is an interesting speculation that there is some possibility that this fluid accumulation, together with the pain-producing vasodilator substance which occurs in it, could be formed as a result of nervous activity. Nobody has been able to show exactly whether this occurs in the migrainous subject, and there is certainly no suggestion why it should occur on one side and not on the other. All this is speculation but I think that the possibility of inhibiting this type of activation of the pain-producing substance is well worth further study. If one could find some drug which would inhibit the process of activation one would be able to see whether it had any therapeutic effect in a subject with migraine.

As far as I am aware, ergotamine has no effect on the development of these pain-producing substances, but if you have vasoconstriction, that will reduce the amount of protein-rich fluid which will escape from the plasma into the tissues, and vasoconstrictors might act by diminishing the amount of materials available for activation.

Perhaps I should add that I myself never had any relief from ergotamine.

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THE PLACE OF ALLERGY IN MIGRAINE

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Before starting my paper I should like to take this opportunity to thank Professor Keele for giving such a lucid explanation of the late Professor Woolf's work. We have all listened with interest to the previous speakers today, and while a few of us are still depressed, many, I think, see some glimmer of hope.

Whether one has special interest in the more conservative work of Macdonald Critchley, the basilar artery involvement investigated by Bickerstaff, those severe migraine attacks ending in a generalized convulsion described by Brain, or the water retention studied by Campbell and Hay, or, especially, in those cases of menstrual migraine written about by Raymond Greene, everyone must realize